

**Protocol title: A Multi-Center, Randomized, Double-Blind, Parallel-Group, Controlled Study to Assess the Efficacy, Safety and Tolerability of Oral DFD-29 Extended Release Capsules for the Treatment of Inflammatory Lesions of Rosacea over 16 weeks**

Protocol ID	DFD-29-CD-002
QPS study code	160382
Authors	Dr. Jessica Prattner Dr. Martina Brandner
Document type	Clinical Study Protocol
Study Phase	2
Document status/version	final, Amendment IV
Date	02 October 2018
EudraCT number	2016-003197-41

**Confidentiality Statement**

The information contained in this document, especially unpublished data, is the property of the sponsor of this study, Dr. Reddy's. It is therefore provided to you in confidence as an investigator, potential investigator, or consultant, for review by you, your staff, and an Ethics Committee or Institutional Review Board. It is understood that this information will not be disclosed to others without written authorization from Dr. Reddy's, except to the extent necessary to obtain informed consent from those persons to whom the study drug may be administered.

## KEY STUDY FACILITIES

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QPS: 160382  
Sponsor: DFD-29-CD-002

Clinical Study Protocol  
02 October 2018, Amendment IV



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QPS: 160382  
Sponsor: DFD-29-CD-002

Clinical Study Protocol  
02 October 2018, Amendment IV



## 1 SIGNATURE PAGE

Investigational product name  
DFD-29 (minocycline HCl) Extended Release Capsules

Protocol number  
DFD-29-CD-002

**Sponsor:**  
Dr. Usha Ranganathan, MD  
Associate Director Clinical  
Development  
Dr. Reddy's Laboratories Ltd.,

  
\_\_\_\_\_  
Signature

4 Oct '2018  
Date

**CRO:**  
Robert Wronski, Ph.D., MBA  
QPS – Director Clinical Research  
Services

  
\_\_\_\_\_  
Signature

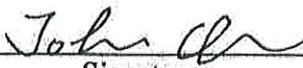
8 Oct. 2018  
Date

Jessica Prattner, PhD  
QPS – Medical Writer

  
\_\_\_\_\_  
Signature

8 Oct 2018  
Date

John Chen  
QPS – Statistician

  
\_\_\_\_\_  
Signature

08 Oct 2018  
Date

## 2 SIGNATURE PAGE FOR INVESTIGATOR

Investigational product name  
DFD-29 (minocycline HCl) Extended Release Capsules

Protocol number  
DFD-29-CD-002

I agree to the terms and conditions relating to this study as defined in this Study Protocol, electronic Case Report Form (eCRF), and any other protocol-related documents. I fully understand that any changes instituted by the investigator(s) without previous agreement with the sponsor would constitute a violation of the study protocol, including any ancillary studies or procedures performed on study subjects (other than those procedures necessary for the well-being of the subjects).

I agree to conduct this study in accordance with the Declaration of Helsinki and its amendments, International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines and applicable regulations and laws. In particular, I will obtain approval by an Ethics Committee or Institutional Review Board (EC/IRB) prior to study start and signed informed consent from all subjects included in this study. In addition, I will allow direct access to source documents and agree to inspection by auditors from the sponsor and Health Authorities. I will ensure that the study drug(s) supplied by the sponsor are being used only as described in this protocol. Furthermore, I confirm herewith that the sponsor is allowed to enter and utilize my professional contact details and function in an electronic database for internal purposes and for submission to worldwide Health Authorities.

Name (print)  
Principal Investigator

\_\_\_\_\_  
Signature

\_\_\_\_\_  
Date

Name institution (print)

\_\_\_\_\_

## PROTOCOL CHANGES LOG

**Amendment IV, dated 02 October 2018**, Amendment III, dated 26 February 2018, Amendment II, dated 01 August 2017, Amendment I issued 29 May 2017.

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20EC of the European Parliament and the Council of the European Union.

An additional analysis set, the Full Analysis Set (FAS), was defined in the study protocol. In addition to the changes stated below, minor typographic errors have been corrected.

Section Reference	Old text	Amended text
<b>Header and Title page</b>	Clinical Study Protocol 26 February 2018, Amendment III	Clinical Study Protocol <del>26 February 2018, Amendment III</del> 02 October 2018, Amendment IV
<b>Section 8.3.2 Study Drug Supply and Packaging</b>	DFD-29 (minocycline HCl) Extended Release Capsules and placebo for DFD-29 will be supplied by Dr. Reddy's Laboratories as 30 count in HDPE bottle. The study drug will be imported by QPS and further managed by ABF	DFD-29 (minocycline HCl) Extended Release Capsules and placebo for DFD-29 will be supplied by Dr. Reddy's Laboratories as <del>30</del> 25 count in HDPE bottle. The study drug will be imported by QPS and further managed by ABF.
<b>Section 10.2 Analysis Population</b>	Four different analysis sets are defined. Subjects who withdraw from the study, or who have missing data, will be included in the statistical analyses provided that they are eligible for inclusion in the analysis population as described below.  <b>Intention to treat population:</b> This analysis population includes all subjects who have been randomized and dispensed the study drug.	Four different analysis sets are defined. Subjects who withdraw from the study, or who have missing data, will be included in the statistical analyses provided that they are eligible for inclusion in the analysis population as described below.  <b>Full analysis set (FAS):</b> <u>This analysis population includes all subjects who have been randomized and had at least one post baseline efficacy assessment. The FAS population will</u>

	<p><b>Safety population:</b> This analysis population includes subjects who had at least one safety assessment post-baseline. The safety population will be employed in the analysis of tolerability and safety variables.</p> <p><b>Per-protocol population:</b> This analysis population comprises all subjects who did not violate the protocol in a way that might affect the evaluation of the effect of the study drug(s) on the primary endpoint, i.e., without major protocol violations or deviations.</p>	<p><u>be the primary population for the efficacy analyses.</u></p> <p><b>Intention to treat population (ITT):</b> This analysis population includes all subjects who have been randomized and dispensed the study drug.</p> <p><b>Safety population:</b> This analysis population includes subjects who had at least one safety assessment post-baseline. The safety population will be employed in the analysis of tolerability and safety variables.</p> <p><b>Per-protocol population (PP):</b> This analysis population comprises all subjects who did not violate the protocol in a way that might affect the evaluation of the effect of the study drug(s) on the primary endpoint, i.e., without major protocol violations or deviations.</p>
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**Amendment III, dated 26 February 2018**, Amendment II, dated 01 August 2017, Amendment I issued 29 May 2017,

This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20EC of the European Parliament and the Council of the European Union.

Some of the available study medication kits are expiring on July 31<sup>st</sup> 2018 and stratification of the randomization per site and IGA score resulted in a high number of kits to be stored at the individual study sites. In order to be able to use up the study medication kits with limited stability, the amount of kits on site needs to be reduced thus the stratification by IGA score is dropped.

All changes made in the course of this amendment are stated in the table below.

Section Reference	Old text	Amended text
<b>Header and Title page</b>	Clinical Study Protocol 01 August 2017, Amendment II	Clinical Study Protocol <del>01 August 2017, Amendment II,</del> 26 February 2018, Amendment III
<b>Key Study Facilities</b>	Dr. Srinivas Shenoy B., MBBS, MD, Principal Scientist- Clinical Studies Dr. Reddy's Laboratories Ltd Innovation Plaza, Survey No.s 42, 45, 46 and 54, Bachupally, Qutbullapur Mandal, R.R. District, Telengana, 500 090 India Phone: +91-40-4434 6126 (Direct) srinivasshenoyb@drreddys.com	<u>Dr. Usha Ranganathan, MD, Associate Director Clinical Development</u> <u>Dr. Reddy's Laboratories Ltd</u> <u>Princeton, NJ 08540</u> <u>United States of America</u> <u>Phone: +1-609 4557 138 (Direct)</u> <u>uranganathan@drreddys.com</u>
<b>Signature page</b>	Dr. Srinivas Shenoy B., MD, Principal Scientist- Clinical Development, Proprietary Products R & D, Dr. Reddy's Laboratories Ltd., India  Denise Montagne, QPS – Statistician	<u>Dr. Usha Ranganathan, MD, Associate Director Clinical Development of</u> <u>Dr. Reddy's Laboratories Ltd.</u>  <u>John Chen, QPS – Statistician</u>
<b>8.6.2 Treatment Assignment</b>	Randomization will be stratified per site and per IGA score (score above or equal to 2) at Baseline.	Randomization will be stratified per site. <u>The first randomizations</u> <u>(approximately 40% of the patients) were also stratified per IGA score.</u> <u>This stratification resulted in a high amount of study medication kits to be</u> <u>stored at the site, limiting the overall availability of unexpired kits in the</u> <u>study. Therefore, stratification per IGA score is dropped and</u> <u>randomization is only stratified per site per IGA score (score above or</u>

		equal to 2) at Baseline
<b>Section 8.6.4: Emergency Procedure for Unblinding</b>	Documentation about any code break must be documented and attached to the eCRF.	<del>Documentation about any code break must be documented and attached to the eCRF.</del> Every code break must be documented.

**Amendment II**, dated **01 August 2017**, Amendment I issued 29 May 2017,

This amendment is considered to be non-substantial based on the criteria set forth in Article 10(a) of Directive 2001/20EC of the European Parliament and the Council of the European Union.

The Study medication label was updated with regard to the amount contained in a bottle, contact information, storage conditions and overall information content of the label. Instead of Annex 13 to the Current Edition of the Good Manufacturing Practices Guidelines Drugs Used in Clinical Trials (GUI-0036) GCP guideline is followed.

In addition to the changes stated below (additions are underlined, removals are crossed out), minor typographic errors have been corrected.

Section Reference	Old text	Amended text
<b>Header and Title page</b>	Clinical Study Protocol 29 May 2017, Amendment I Study Phase II	Clinical Study Protocol <del>29 May 2017</del> <u>01 August 2017</u> , Amendment II Study Phase <del>II</del>
<b>8.1.3.7: Laboratory Assessments</b>	As a rule, the blood samples will be taken from the subject by puncture of a vein in the cubital or the antebrahial region. Samples will be collect under fasted conditions (at least 8 hours).	As a rule, the blood samples will be taken from the subject by puncture of a vein in the cubital or the antebrahial region. <del>Samples will be collect under fasted conditions (at least 8 hours).</del>
<b>8.3.2: Study Drug Supply and Packag ing</b>	... containing 30 capsules. The medication bottles will be labeled according to ABF's procedure as stated in Section <u>8.3.3</u> See sample label  The clinical labelled study drug will be supplied to the investigational sites in HDPE bottle packs of 30 units for each strength of DFD-29 (minocycline HCl) Extended Release Capsules (20 mg and 40 mg), Oraycea® (doxycycline) Modified Release Hard Capsules and placebo.  One reserve bottle with 30 units will be available for each subject. This bottle will be provided on Day 1.	... containing <del>30</del> <u>25</u> capsules. The medication bottles will be labeled according to ABF's procedure as stated in Section <u>8.3.3</u> See sample label, <u>Figure 8-1</u> .  The clinical labelled study drug will be supplied to the investigational sites in HDPE bottle packs of <del>30</del> <u>25</u> units <del>for</del> . <u>Boxes containing 6 bottles of each strength of DFD-29 (minocycline HCl) Extended Release Capsules (20 mg and 40 mg), Oraycea® (doxycycline) Modified Release Hard Capsules and placebo will be provided as individual subject kits. The six bottles in each individual subject kit are numbered consecutively. From the kit, two consecutively numbered bottles will be provided to the subjects during visits 2-5, starting with the lowest number available. Subjects will be instructed to always take the capsules from the bottle with the lowest</u>

		<p><u>number, until the same is empty and then start with the other bottle. Both bottles received by subject during a visit, whether unused, partially used or empty, must be returned to the study staff at the successive visit, who will verify the accountability of the IMPs. Partially used bottles will be re-dispensed at the successive visit, while emptied bottles will be replaced with the next bottle from the kit bearing the lowest available number.</u></p> <p><del>One reserve bottle with 30 units will be available for each subject. This bottle will be provided on Day 1.</del></p> <p><b><u>Figure 8-1: Flowchart for dispensing and returning study medication</u></b></p>
<p><b>8.3.3: Study Drug Labeling</b></p>	<p>...and regulations, especially Annex 13 to the Current Edition of the Good Manufacturing Practices Guidelines Drugs Used in Clinical Trials (GUI-0036). The labels...</p> <p>The labels will be in German and Dutch language. An English version will be available for review purposes.</p> <ul style="list-style-type: none"> <li>• Study number (DFD-29-CD-002)</li> <li>• Study drug (30x DFD-29 10 mg / 20 mg / 40 mg / placebo Capsules)</li> <li>• Visit number or ‘Reserve Bottle’</li> <li>• Name of Investigator</li> </ul>	<p><del>...and regulations, especially Annex 13 to the Current Edition of the Good Manufacturing Practices Guidelines Drugs Used in Clinical Trials (GUI-0036). The labels...</del></p> <p>The labels will be in German <del>and Dutch</del> language. An English version will be available for review purposes.</p> <ul style="list-style-type: none"> <li>• Study number (DFD-29-CD-002)</li> <li>• Study drug (<del>30</del><u>25</u>x DFD-29 20 mg / 40 mg / placebo / <u>Oraycea</u><sup>®</sup> Capsules)</li> <li>• <del>Visit</del><u>Bottle</u> number or ‘Reserve Bottle’</li> <li>• <del>Name of Investigator</del></li> </ul>
<p><b>Figure 8-2: Sample Label</b></p>	<p><b>Bottle Label</b></p> <p>Prüfplancode: DFD-29-CD-002</p> <p>EudraCT Nr.: 2016-003197-41</p> <p>Sponsor: Dr. Reddy’s Laboratories Ltd., India; 8-2-337, Road No. 3, Banjara Hills, Hyderabad; Telangana</p>	<p><b><u>Bottle Label Text</u></b></p> <p><u>Figure 8-2: Sample Label</u></p> <p>Prüfplancode: DFD-29-CD-002</p> <p>EudraCT Nr.: 2016-003197-41</p> <p>Sponsor: Dr. Reddy’s Laboratories Ltd., India; 8-2-337, Road No. 3, Banjara Hills, Hyderabad; Telangana 500034, India; Tel: <del>00-91-40-4900</del></p>

	<p>500034, India; Tel: +91-40-4900 2900</p> <p>CRO: QPS Austria GmbH; Parkring 12; 8074 Grambach, Austria; Tel.:+43 316 258 111</p> <p>Inhalt: 30 Kapseln 20 mg Minocyclin oder 40 mg Minocyclin oder 40 mg Oracea oder Placebo zur oralen Anwendung</p> <p>Nach Anweisung des Prüfarztes anwenden.</p> <p>Lagerung bei 15°C -25°C.</p> <p>Für Kinder unzugänglich aufbewahren.</p> <p>Nur zur klinischen Prüfung bestimmt.</p> <p>Nicht verbrauchte Kapseln und leere Flaschen sind spätestens beim letzten Studienbesuch zurückzugeben.</p> <p>Ch.-B.: XXXXX</p> <p>Verwendbar bis: MM/YYYY</p> <p>Kitnr.: XXXX</p> <p>Flasche [X] X = 1 oder 2 oder 3 oder 4 oder Reserve</p> <p>Patientennr.: _____</p> <p><b>Box Label</b></p>	<p><del>29004434-6126</del></p> <p>CRO: QPS Austria GmbH; Parkring 12; 8074 Grambach, Austria; Tel.:+43 316 258 111</p> <p>Inhalt: <del>30</del><u>25</u> Kapseln 20 mg Minocyclin oder 40 mg Minocyclin oder 40 mg Oracea oder Placebo zur oralen Anwendung</p> <p>Nach Anweisung des Prüfarztes anwenden.</p> <p>Lagerung bei <del>15°C -25°C</del><u>25°C</u>. <u>Temperaturabweichungen zwischen 15°C - 30°C sind erlaubt.</u></p> <p>Für Kinder unzugänglich aufbewahren.</p> <p>Nur zur klinischen Prüfung bestimmt.</p> <p><u>Geöffnete Flaschen sind innerhalb von 30 Tagen zu verbrauchen.</u></p> <p>Nicht verbrauchte Kapseln und leere Flaschen sind spätestens beim letzten Studienbesuch zurückzugeben.</p> <p>Ch.-B.: XXXXX</p> <p>Verwendbar bis: MM/YYYY</p> <p>Kitnr.: XXXX</p> <p>Flasche [X] X = 1 oder 2 oder 3 oder 4 oder <del>Reserve</del><u>5 oder 6</u></p> <p>Patientennr.: _____</p> <p><b>Box Label <u>Text</u></b></p>
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	<p>Prüfplancode: DFD-29-CD-002</p> <p>EudraCT Nr.: 2016-003197-41</p> <p>Sponsor: Dr. Reddy's Laboratories Ltd., India; 8-2-337, Road No. 3, Banjara Hills, Hyderabad; Telangana 500034, India; Tel: +91-40-4900 2900</p> <p>CRO: QPS Austria GmbH; Parkring 12; 8074 Grambach, Austria; Tel.:+43 316 258 111 340</p> <p>Inhalt: 5 Flaschen zu je 30 Kapseln 20 mg Minocyclin oder 40 mg Minocyclin oder 40 mg Oraycea® oder Placebo zur oralen Anwendung</p> <p>Nach Anweisung des Prüfarztes anwenden.</p> <p>Lagerung bei 15°C -25°C.</p> <p>Für Kinder unzugänglich aufbewahren.</p> <p>Nur zur klinischen Prüfung bestimmt.</p> <p>Nicht verbrauchte Kapseln und leere Flaschen sind spätestens beim letzten Studienbesuch zurückzugeben.</p> <p>Ch.-B.: XXXXX</p> <p>Verwendbar bis: MM/YYYY</p> <p>Kitnr.: XXXX</p> <p>Patientenr.: _____</p> <p>Figure 8-1: Sample Label</p>	<p>Prüfplancode: DFD-29-CD-002</p> <p>EudraCT Nr.: 2016-003197-41</p> <p>Sponsor: Dr. Reddy's Laboratories Ltd., India; 8-2-337, Road No. 3, Banjara Hills, Hyderabad; Telangana 500034, India; Tel: <del>+Tel: 00-91-40-4900-2900</del><u>4434-6126</u></p> <p>CRO: QPS Austria GmbH; Parkring 12; 8074 Grambach, Austria; Tel.:+43 316 258 111-<del>340</del></p> <p>Inhalt: <del>56</del> Flaschen zu je <del>3025</del> Kapseln 20 mg Minocyclin oder 40 mg Minocyclin oder 40 mg Oraycea® oder Placebo zur oralen Anwendung</p> <p>Nach Anweisung des Prüfarztes anwenden.</p> <p>Lagerung bei <u>25°C</u>. <u>Temperaturabweichungen zwischen 15°C -2530°C sind erlaubt.</u></p> <p>Für Kinder unzugänglich aufbewahren.</p> <p>Nur zur klinischen Prüfung bestimmt.</p> <p><u>Geöffnete Flaschen sind innerhalb von 30 Tagen zu verbrauchen.</u></p> <p>Nicht verbrauchte Kapseln und leere Flaschen <del>sind spätestens beim letzten</del><u>bei jedem</u> Studienbesuch zurückzugeben.</p> <p>Ch.-B.: XXXXX</p> <p>Verwendbar bis: MM/YYYY</p> <p>Kitnr.: XXXX</p>
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		Patientennr.: _____ Figure 8-1: Sample Label
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**Amendment I**, dated 29 May 2017, original Protocol issued 21 November 2016

This amendment is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20EC of the European Parliament and the Council of the European Union.

The 4 treatment arms in the study were changed from 10 mg, 20 mg, 40 mg DFD-29 (minocycline HCL) and placebo to 20 mg and 40 mg DFD-29 (minocycline HCL), 40 mg Oraycea<sup>®</sup> (doxycycline) and placebo. In addition to the changes stated below, minor typographic errors have been corrected.

Section Reference	Old text	Amended text
<b>Header</b>	Clinical Study Protocol 21 November 2016, Version 2	Clinical Study Protocol 29 May 2017, Amendment I
<b>Title page</b>	Protocol title: A Multi-Center, Randomized, Double-Blind, Parallel-Group, Placebo-Controlled Study to Assess the Efficacy, Safety and Tolerability of Oral DFD-29 (minocycline HCL) Extended Release Capsules Compared to Placebo for the Treatment of Inflammatory Lesions of Rosacea over 16 weeks	Protocol title: A Multi-Center, Randomized, Double-Blind, Parallel-Group, <del>Placebo</del> -Controlled Study to Assess the Efficacy, Safety and Tolerability of Oral DFD-29 ( <del>minocycline HCL</del> ) Extended Release Capsules <del>Compared to Placebo</del> for the Treatment of Inflammatory Lesions of Rosacea over 16 weeks
<b>Title page</b>	Clinical Study Protocol 21 November 2016, Version 2	Clinical Study Protocol 29 May 2017, Amendment I
<b>Key Study Facilities CRO</b>	QPS Netherlands B.V. Clinical Research Europe Petrus Campersingel 123 9713 AG Groningen, the Netherlands	QPS Austria Parkring 12 8074 Grambach, Austria
<b>Key Study Facilities Pharmacy</b>	QPS Netherlands B.V. Clinical Research Europe Petrus Campersingel 123 9713 AG Groningen, the Netherlands	ABF Pharmaceutical Services GmbH Gastgebgsasse 5-13 1230 Vienna, Austria Phone +43 1 890 12 00 20 Email: Martin.Zepetzauer@abf-pharma.com
<b>Section 1: Signature Page</b>	CRO Jan Bart Hak, PhD, QPS, Director of Clinical Research Europe	CRO Robert Wronski, Ph.D., MBA QPS – Director Clinical Research Services

<b>Section 4: List of Abbreviations</b>		updated
<b>Section 5: Synopsis, Centers / Countries</b>	15 centers: The Netherlands, Germany	At least 15 centers in Germany
<b>Section 5: Synopsis, Investigational Product and Dosage Forms</b>	DFD-29 (minocycline HCl) Extended Release Capsules containing minocycline hydrochloride equivalent to 10 mg, 20 mg and 40 mg of minocycline.	DFD-29 (minocycline HCl) Extended Release Capsules containing minocycline hydrochloride equivalent to 20 mg and 40 mg of minocycline.
<b>Section 5: Synopsis, Comparative Product and Dosage Forms</b>	Placebo capsules	Placebo capsules Oraycea <sup>®</sup> modified release hard capsules containing 40 mg of anhydrous doxycycline
<b>Section 5: Synopsis, Objectives</b>	<p>To evaluate the efficacy of multiple strengths of oral DFD-29 (minocycline 10 mg, 20 mg and 40 mg capsules) in comparison to placebo in the treatment of inflammatory lesions of rosacea for 16 weeks.</p> <p>To evaluate the safety and tolerability of multiple strengths of oral DFD-29 in comparison to placebo in the treatment of inflammatory lesions of rosacea for 16 weeks.</p>	<p><b>Primary Objectives:</b></p> <ul style="list-style-type: none"> <li>To evaluate the efficacy of <del>multiple strengths of</del> oral DFD-29 (minocycline <del>10 mg, 20 mg and</del> HCl 40 mg capsules) in comparison to placebo in the treatment of inflammatory lesions of rosacea for 16 weeks</li> <li>To evaluate the safety and tolerability of <del>multiple strengths of</del> oral DFD-29 (<u>minocycline HCl 40 mg capsules</u>) in comparison to placebo in the treatment of inflammatory lesions of rosacea for 16 weeks.</li> </ul> <p><b>Secondary Objectives:</b></p> <ul style="list-style-type: none"> <li><u>To evaluate the efficacy of oral DFD-29 (minocycline HCl 20 mg capsules) in comparison to placebo in the treatment of inflammatory lesions of rosacea for 16 weeks</u></li> <li><u>To evaluate the efficacy of the two dosage strengths of oral DFD-29 (minocycline HCl 20 mg and 40 mg capsules) in comparison to Oraycea<sup>®</sup> (doxycycline 40 mg capsules) in the treatment of</u></li> </ul>

		<p><u>inflammatory lesions of rosacea for 16 weeks.</u></p> <ul style="list-style-type: none"> <li>• <u>To evaluate the safety and tolerability of oral DFD-29 (minocycline HCl 20 mg capsules) in comparison to placebo in the treatment of inflammatory lesions of rosacea for 16 weeks.</u></li> <li>• <u>To evaluate the safety and tolerability of the two dosage strengths of oral DFD-29 (minocycline HCl 20 mg and 40 mg capsules) in comparison to Oraycea<sup>®</sup> (doxycycline 40 mg capsules) in the treatment of inflammatory lesions of rosacea for 16 weeks.</u></li> <li>• <u>To evaluate the efficacy of oral DFD-29 (minocycline HCl 40 mg capsules) in comparison to oral DFD-29 (minocycline HCl 20 mg capsules) in the treatment of inflammatory lesions of rosacea for 16 weeks.</u></li> <li>• <u>To evaluate the safety and tolerability of oral DFD-29 (minocycline HCl 40 mg capsules) in comparison to DFD-29 (minocycline HCl 20 mg capsules) in the treatment of inflammatory lesions of rosacea for 16 weeks.</u></li> </ul>
<p><b>Section 5: Synopsis, Design</b></p>	<p>This is a 16-week, multicenter, placebo-controlled, randomized, parallel group, double-blind study. Subjects, who are at least 18 years old, diagnosed with papulopustular rosacea will be randomized to 4 different treatment groups.</p>	<p>This is a 16-week, multicenter, <del>placebo</del>-controlled, randomized, parallel group, double-blind study. Subjects, who are at least 18 years old, diagnosed with papulopustular rosacea will be randomized to 4 different treatment groups.</p>
<p><b>Section 5: Synopsis, Treatments</b></p>	<ol style="list-style-type: none"> <li>1. DFD-29 (minocycline HCl) Extended Release Capsules (10 mg) once daily for 16 weeks</li> <li>2. DFD-29 (minocycline HCl) Extended Release Capsules (20 mg) once daily for 16 weeks</li> <li>3. DFD-29 (minocycline HCl) Extended Release Capsules (40 mg) once daily for 16 weeks</li> <li>4. Placebo for DFD-29 Capsules once daily for 16 weeks</li> </ol>	<p>Each subject will be allocated to one of the following treatment groups, receiving 1 capsule once daily in the morning for 16 weeks:</p> <ol style="list-style-type: none"> <li>1. DFD-29 (minocycline HCl) Extended Release Capsules (40 mg)</li> <li>2. DFD-29 (minocycline HCl) Extended Release Capsules (20 mg)</li> <li>3. <u>Oraycea<sup>®</sup> (doxycycline) Modified Release Hard Capsules (40 mg)</u></li> <li>4. Placebo Capsules</li> </ol>

<b>Section 5: Synopsis, Summary of Study Design</b>	...and collection of adverse event data.		...and collection of adverse event data. <u>Impact of the treatment on the Quality of Life (QOL) of the subjects will be done using a rosacea specific tool RosaQol at Baseline, and at weeks 4, 8, 12 and 16.</u>																																																																
<b>Section 5: Synopsis, Inclusion criteria</b>	3. Subjects, any gender or ethnicity (Fitzpatrick skin type I – III), must be in good general health as determined by the Investigator.		3. Subjects, any gender or ethnicity (and of Fitzpatrick skin type I – III), must be in good general health as determined by the Investigator.																																																																
<b>Section 5: Synopsis, Concomitant Medication Table</b>	<table border="1"> <tr> <td data-bbox="450 549 813 611">Other systemic drugs used for treatment of rosacea</td> <td data-bbox="813 549 954 611">30 days</td> <td data-bbox="954 549 1133 611">Prohibited</td> </tr> <tr> <td data-bbox="450 611 813 799">Antacids containing calcium, magnesium or aluminum, Iron preparations, bismuth subsalicylate</td> <td data-bbox="813 611 954 799">Not applicable</td> <td data-bbox="954 611 1133 799">Restricted for 1.5 hours before to 3.0 hours after ingestion of IP</td> </tr> <tr> <td colspan="3" data-bbox="450 799 1133 834"><b>Others</b></td> </tr> <tr> <td data-bbox="450 834 813 1114">Facial procedures such as chemical peel, photodynamic therapy, acne surgery, cryodestruction or chemodestruction, x-ray therapy, intralesional steroids, dermabrasion, or depilation (except eyebrow shaping)</td> <td data-bbox="813 834 954 1114">45 days</td> <td data-bbox="954 834 1133 1114">Prohibited</td> </tr> <tr> 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(Diphenylhydantoin)</u></td> <td data-bbox="1731 1313 1843 1345"><u>30 days</u></td> <td data-bbox="1843 1313 2047 1345"><u>Prohibited</u></td> </tr> </table>		<u>Systemic retinoid (including high dose vitamin A &gt;10,000 units per day)</u>	180 days	Prohibited	Other systemic drugs used for treatment of rosacea	30 days	Prohibited	<u>Antacids containing calcium, magnesium or aluminum, Iron preparations, bismuth subsalicylate</u>	Not applicable	Restricted for 1.5 hours before to 3.0 hours after ingestion of IP	<b>Others</b>			<u>Facial procedures such as chemical peel, photodynamic therapy, acne surgery, cryodestruction or chemodestruction, x ray therapy, intralesional steroids, dermabrasion, or depilation (except eyebrow shaping)</u>	45 days	Prohibited	<u>Laser therapy or Intense Pulse Light Treatment</u>	45 days	Prohibited	<u>Other procedures on face (Thermage® etc)</u>	45 days	Prohibited	<u>Other investigational product or device</u>	90 days	Prohibited				<u>Other systemic drugs used 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		<u>Primidone</u>	<u>30 days</u>	<u>Prohibited</u>
		<u>Cyclosporin</u>	<u>30 days</u>	<u>Prohibited</u>
		<u>Methoxyflurane</u>	<u>30 days</u>	<u>Prohibited</u>
<b>Section 5: Synopsis, Primary Efficacy Endpoints</b>	<p><b>Co-Primary endpoints:</b></p> <ul style="list-style-type: none"> <li>Proportion of subjects with IGA (modified scale without erythema) success – Grade 0 or 1 at the end of study with at least 2 grade reduction from Baseline to Week 16.</li> <li>Total inflammatory lesion count (sum of papules, pustules, and nodules) reduction from Baseline to Week 16.</li> </ul>	<p><b>Co-Primary endpoints:</b></p> <ul style="list-style-type: none"> <li>Proportion of subjects with IGA (modified scale without erythema) <del>success</del> <u>'treatment success'</u> – Grade 0 or 1 at the end of study with at least 2 grade reduction from Baseline to Week 16.</li> <li>Total inflammatory lesion count (sum of papules, pustules, and nodules) reduction from Baseline to Week 16.</li> </ul>		
<b>Section 5: Synopsis, Secondary Efficacy Endpoints</b>	<ul style="list-style-type: none"> <li>Proportion of subjects with at least a two grade improvement of IGA (modified scale without erythema) grade from Baseline to Week 16.</li> <li>Change in clinician's erythema assessment (CEA) score from Baseline to Week 16.</li> <li>Total inflammatory lesion count reduction from Baseline compared to Weeks 4, 8 and 12.</li> <li>Percentage reduction in total inflammatory lesion count from Baseline to Week 16.</li> <li>Change in Telangiectasia score from Baseline to Week 16.</li> </ul>	<ul style="list-style-type: none"> <li>Proportion of subjects with at least a <del>two</del> 2 grade <del>improvement</del> <u>reduction in</u> IGA (modified scale without erythema) <del>grade</del> <u>'treatment success'</u> <del>score</del> from Baseline to Week 16.</li> <li><del>Change in clinician's erythema assessment (CEA) score from Baseline to Week 16.</del></li> <li><del>Total inflammatory lesion count reduction from Baseline compared to Weeks 4, 8 and 12.</del></li> <li><del>Percentage reduction</del> <u>Median change</u> in total inflammatory lesion count from Baseline to Week 16.</li> <li><del>Change in Telangiectasia</del> <u>RosaQol</u> score from Baseline to Week 16.</li> </ul>		
<b>Section 5: Synopsis, Exploratory Efficacy Endpoints</b>	<ul style="list-style-type: none"> <li>Mean change in high sensitivity C-reactive protein (hs-CRP) levels from Baseline compared to Week 16.</li> <li>Proportion of subjects meeting CEA treatment success criteria (i.e. a two grade improvement in the CEA scale) at weeks 4, 8, and 12.</li> <li>Proportion of subjects meeting IGA treatment success criteria (i.e. a two grade improvement in the IGA scale) at weeks 4, 8, and 12.</li> <li>Proportion of subjects meeting the CEA treatment success criteria at the end of the study will be</li> </ul>	<ul style="list-style-type: none"> <li><u>Proportion of subjects with IGA (modified scale without erythema) 'treatment success' from Baseline to Weeks 4, 8 and 12.</u></li> <li><u>Total inflammatory lesion count (sum of papules, pustules, and nodules) reduction from Baseline to Weeks 4, 8 and 12.</u></li> <li><u>Proportion of subjects with at least a 2 grade reduction in IGA (modified scale without erythema) score from baseline to week 4,8 and 12.</u></li> <li><u>Median change in total RosaQol score from Baseline to Weeks 4, 8 and 12.</u></li> <li>Mean change in high sensitivity C-reactive protein (hs-CRP) levels</li> </ul>		

	<p>compared between placebo, the 10 mg, 20 mg, and 40 mg dose levels of DFD-29.</p> <ul style="list-style-type: none"> <li>• Proportion of subjects meeting the IGA treatment success criteria at the end of the study will be compared between placebo, the 10 mg, 20 mg, and 40 mg dose levels of DFD-29.</li> <li>• Comparison of the above-mentioned efficacy parameters between two dose levels (i.e. 40 mg vs 20 mg, 40 mg vs 10 mg, and 20 mg vs 10 mg) of DFD-29.</li> </ul>	<p>from Baseline compared to Week 16.</p> <ul style="list-style-type: none"> <li>• <u>Change in Telangiectasia score from Baseline compared to Week 16.</u></li> <li>• Proportion of subjects meeting CEA ‘treatment success’ criteria (i.e. a two grade improvement in the CEA scale) at weeks 4, 8, 12 and 16.</li> <li><del>• Proportion of subjects meeting IGA treatment success criteria (i.e. a two grade improvement in the IGA scale) at weeks 4, 8, and 12.</del></li> <li><del>• Proportion of subjects meeting the CEA treatment success criteria at the end of the study will be compared between placebo, the 10 mg, 20 mg, and 40 mg dose levels of DFD-29.</del></li> <li><del>• Proportion of subjects meeting the IGA treatment success criteria at the end of the study will be compared between placebo, the 10 mg, 20 mg, and 40 mg dose levels of DFD-29.</del></li> <li>• Comparison of the above mentioned efficacy parameters between two dose levels (i.e. 40 mg vs 20 mg, 40 mg vs 10 mg, and 20 mg vs 10 mg) of DFD-29.</li> </ul>
<p><b>Synopsis, Statistical Methodology</b></p>	<p>Safety and tolerability data will be listed individually and summarized using descriptive statistics and frequency tables. Shifts in mean clinical laboratory parameters and vital sign parameters at Week 16 as compared to Baseline, will be computed and analyzed.</p>	<p>Safety and tolerability data will be listed individually and summarized using descriptive statistics and frequency tables. <del>Shifts in mean clinical laboratory parameters and vital sign parameters at Week 16 as compared to Baseline, will be computed and analyzed.</del> <u>Change from Baseline will be analyzed for the following parameters:</u></p> <ul style="list-style-type: none"> <li>• <u>Change from baseline to each scheduled time point up to EOS for vital signs compared between DFD-29, Oraycea<sup>®</sup> and placebo.</u></li> <li>• <u>Change from Screening up to EOS for physical examination compared between DFD-29, placebo and Oraycea<sup>®</sup>.</u></li> <li>• <u>Change from Screening up to EOS for clinical laboratory tests compared between DFD-29 Oraycea<sup>®</sup> and placebo.</u></li> <li>• <u>Treatment-emergent AEs up to EOS compared between DFD-29, Oraycea<sup>®</sup> and placebo.</u></li> <li>• <u>Treatment-emergent AEs leading to premature discontinuation of study drug compared between DFD-29, Oraycea<sup>®</sup> and placebo.</u></li> <li>• <u>Treatment-emergent SAEs up to EOS compared between DFD-29,</u></li> </ul>

	<p><b>Efficacy</b></p> <p>Co-Primary endpoints:</p> <ul style="list-style-type: none"> <li>The proportion of subjects with IGA (modified scale without erythema) success – will be investigated with a Chi-square test for placebo versus active treatment. Success is described as having at least 2 grade reduction from baseline with grade 0 or 1 at the end of the study.</li> <li>The difference between placebo and active treatment will be tested for the total inflammatory lesion count reduction from baseline at week 16 with a MIXED Model, with the investigator as a random factor.</li> </ul> <p>Secondary endpoints:</p> <ul style="list-style-type: none"> <li>Proportion of subjects with at least a two grade improvement of IGA (modified scale without erythema) grade from Baseline to Week 16 will be investigated with a Chi-square test comparing placebo with active treatment.</li> <li>Change in clinician’s erythema assessment (CEA) score from Baseline to Week 16 will be investigated with an ANOVA comparing placebo with active treatment.</li> <li>The difference between placebo and active treatment will be tested for the total inflammatory lesion count reduction from Baseline, at Weeks 4, 8 and 12 using MIXED Model with the investigator as a random factor.</li> </ul>	<p><u>Oraycea® and placebo.</u></p> <p><b>Efficacy</b></p> <p><u>For all endpoints, the comparison of oral DFD-29 (40 mg capsule) versus placebo will be the primary objective of the study. All other comparisons viz. between oral DFD-29 (20 mg capsule) and placebo, between oral DFD-29 (40 and 20 mg capsules) and Oraycea® and between oral DFD-29 40 mg capsules and DFD-29 20 mg capsules, will be treated as secondary.</u></p> <p><del>Co-Primary endpoints</del> <u>Endpoints:</u></p> <ul style="list-style-type: none"> <li>The proportion of subjects with IGA (modified scale without erythema) <u>treatment</u> success – will be investigated with a Chi-square test <del>for placebo versus active treatment.</del> <u>Treatment</u> Success is described as having at least 2 grade reduction from baseline with grade 0 or 1 at <del>the end of the study</del> <u>Week 16.</u></li> <li>The difference between <del>placebo and active treatment</del> <u>will be tested for the treatments in terms of the change from baseline in the total inflammatory lesion count reduction from baseline at Week 16 with a will be tested using MIXED Model, with the investigator as a random factor.</u></li> </ul> <p><del>Secondary endpoints</del> <u>Endpoints:</u></p> <ul style="list-style-type: none"> <li><u>The proportion of subjects with at least a 2 grade reduction in IGA (modified scale without erythema) score from baseline to week 16, will be investigated with a Chi-square test.</u></li> <li><u>Median change in total RosaQoL score from Baseline to Week 16 will be analyzed using ANOVA.</u></li> </ul> <p><u>Exploratory Endpoints</u></p> <ul style="list-style-type: none"> <li>Proportion of subjects with at least a two grade improvement of IGA (modified scale without erythema) grade from Baseline to <del>Week 16</del></li> </ul>
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	<ul style="list-style-type: none"> <li>Percentage reduction in total inflammatory lesion count from Baseline to Week 16 will be investigated.</li> <li>Change in Telangiectasia score from Baseline to Week 16 will be investigated with an ANOVA comparing placebo with active treatment.</li> </ul> <p>Exploratory endpoints:</p> <ul style="list-style-type: none"> <li>The difference between placebo and active treatment will be tested for the mean change in high sensitivity C-reactive protein (hs-CRP) levels from Baseline to Week 16 using ANOVA.</li> <li>The proportion of subjects meeting the CEA treatment success criteria at Weeks 4, 8, and 12 for placebo versus active treatment will be tested using a Chi-square test.</li> <li>The proportion of subjects meeting the IGA treatment success criteria at Weeks 4, 8, and 12 for placebo versus active treatment will be tested using a Chi-square test.</li> <li>The proportion of subjects meeting the treatment success criteria in terms of CEA at the end of the study will be compared between the 10 mg, 20 mg, and 40 mg dose levels of DFD-29 using a Chi-square test.</li> <li>The proportion of subjects meeting the treatment success criteria in terms of IGA at the end of the study will be compared between the 10 mg, 20 mg, and 40 mg dose levels of DFD-29 using a Chi-square test.</li> <li>Comparison of the above-mentioned exploratory efficacy parameters of the differences between two dose levels (i.e. 40 mg vs 20 mg, 40 mg vs 10 mg,</li> </ul>	<p><u>Weeks 4, 8 12</u> will be investigated with a Chi-square test <del>comparing placebo with active treatment.</del></p> <ul style="list-style-type: none"> <li><del>Change in clinician's erythema assessment (CEA) score from Baseline to Week 16 will be investigated with an ANOVA comparing placebo with active treatment.</del></li> <li>The difference between <del>placebo and active treatment</del> <u>will be tested for treatments in terms of the change from baseline in the total inflammatory lesion count reduction from Baseline</u>, at Weeks 4, 8 and 12 <u>will be tested</u> using MIXED Model with the investigator as a random factor.</li> <li><del>Percentage reduction</del> <u>The proportion of subjects with at least a 2 grade reduction in IGA (modified scale without erythema) score from baseline to week 4, 8 and 12, will be investigated with a Chi-square test.</u></li> <li><u>Median change in total inflammatory lesion count RosaQoL score from Baseline to Weeks 4, 8 and 12 will be investigated using ANOVA.</u></li> <li><del>Change in Telangiectasia score from Baseline to Week 16 will be investigated with an ANOVA comparing placebo with active treatment.</del></li> </ul> <p>Exploratory endpoints:</p> <ul style="list-style-type: none"> <li>The difference between <del>placebo and active treatment</del> <u>treatments</u> will be tested for the mean change in high sensitivity C-reactive protein (hs-CRP) levels from Baseline to Week 16 using ANOVA</li> <li><del>The proportion</del> <u>Change in Telangiectasia score from Baseline to Week 16 will be investigated using ANOVA.</u></li> <li><u>Proportion of subjects meeting the CEA 'treatment success' criteria (i.e. a two grade improvement in the CEA scale) in the treatment groups at Weeks 4, 8, 12 and 12 for placebo versus active treatment will be tested using a Chi-square test.</u></li> <li><del>The proportion of subjects meeting the IGA treatment success criteria at Weeks 4, 8, and 12 for placebo versus active treatment</del> <u>16 will be</u></li> </ul>
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	and 20 mg vs 10 mg) of DFD-29 using ANOVA.	<p><del>tested</del> <u>investigated</u> using a <del>Chi-square test</del> <u>ANOVA</u>.</p> <ul style="list-style-type: none"> <li><del>The proportion of subjects meeting the treatment success criteria in terms of CEA at the end of the study will be compared between the 10 mg, 20 mg, and 40 mg dose levels of DFD-29 using a Chi-square test.</del></li> <li><del>The proportion of subjects meeting the treatment success criteria in terms of IGA at the end of the study will be compared between the 10 mg, 20 mg, and 40 mg dose levels of DFD-29 using a Chi-square test.</del></li> <li><del>Comparison of the above mentioned exploratory efficacy parameters of the differences between two dose levels (i.e. 40 mg vs 20 mg, 40 mg vs 10 mg, and 20 mg vs 10 mg) of DFD-29 using ANOVA.</del></li> </ul> <p><u>Exploratory analyses for the following subgroups will be performed:</u></p> <ul style="list-style-type: none"> <li><u>Male versus female.</u></li> <li><u>Mild (score 2), moderate (score 3) and severe (score 4) IGA score.</u></li> <li><u>Normal hs-CRP versus abnormal hs-CRP at baseline.</u></li> </ul>
<b>Table 1: Visit and Assessment schedule</b>	Demographic data ...	Demographic data <u>including Fitzpatrick Skin Type</u>  <u>RosaQoL Score</u> (added at Day -30 to Day -3, Day 1, Day 29, Day 57, Day 85 and Day 113).
<b>Section 6.2: Study Rational</b>	This is a multi-center, randomized, double-blind, parallel-group, placebo-controlled study to assess the efficacy, safety and tolerability of multiple strengths of oral DFD-29 (minocycline HCl) Extended Release Capsules compared to placebo for the treatment of inflammatory lesions of rosacea for 16 weeks.	This is a multi-center, randomized, double-blind, parallel-group, <del>placebo-controlled</del> study to assess the efficacy, safety and tolerability of <del>multiple</del> <u>two dosage</u> strengths of oral DFD-29 (minocycline HCl) Extended Release Capsules compared to placebo <u>and Oraycea® Modified Release Hard Capsules</u> for the treatment of inflammatory lesions of rosacea for 16 weeks.
<b>Section 6.2.1: Dose Selection</b>	...dose strengths of DFD-29 to be evaluated in this study are 10 mg, 20 mg and 40 mg	...dose strengths of DFD-29 to be evaluated in this study are <del>10 mg,</del> 20 mg and 40 mg
<b>Section 7: Study Objectives</b>	<p><b>Objectives</b></p> <p>To evaluate the efficacy of multiple strengths of oral DFD-29 (minocycline 10 mg, 20 mg and 40 mg capsules) in comparison to placebo in the treatment of inflammatory lesions of rosacea for 16 weeks.</p> <p>To evaluate the safety and tolerability of multiple</p>	<p><b>Primary Objectives:</b></p> <ul style="list-style-type: none"> <li>To evaluate the efficacy of <del>multiple strengths of</del> oral DFD-29 (minocycline <del>10 mg, 20 mg and</del> HCl 40 mg capsules) in comparison to placebo in the treatment of inflammatory lesions of rosacea for 16 weeks</li> <li>To evaluate the safety and tolerability of oral DFD-29 (<u>minocycline</u></li> </ul>

	<p>strengths of oral DFD-29 in comparison to placebo in the treatment of inflammatory lesions of rosacea for 16 weeks.</p>	<p><u>HCl 40 mg capsules</u>) in comparison to placebo in the treatment of inflammatory lesions of rosacea for 16 weeks.</p> <p><b>Secondary Objectives:</b></p> <ul style="list-style-type: none"> <li>• <u>To evaluate the efficacy of oral DFD-29 (minocycline HCl 20 mg capsules) in comparison to placebo in the treatment of inflammatory lesions of rosacea for 16 weeks.</u></li> <li>• <u>To evaluate the efficacy of the two dosage strengths of oral DFD-29 (minocycline HCl 20 mg and 40 mg capsules) in comparison to Oraycea<sup>®</sup> (doxycycline 40 mg capsules) in the treatment of inflammatory lesions of rosacea for 16 weeks.</u></li> <li>• <u>To evaluate the safety and tolerability of oral DFD-29 (minocycline HCl 20 mg capsules) in comparison to placebo in the treatment of inflammatory lesions of rosacea for 16 weeks.</u></li> <li>• <u>To evaluate the safety and tolerability of the two dosage strengths of oral DFD-29 (minocycline HCl 20 mg and 40 mg capsules) in comparison to Oraycea<sup>®</sup> (doxycycline 40 mg capsules) in the treatment of inflammatory lesions of rosacea for 16 weeks.</u></li> <li>• <u>To evaluate the efficacy of oral DFD-29 (minocycline HCl 40 mg capsules) in comparison to oral DFD-29 (minocycline HCl 20 mg capsules) in the treatment of inflammatory lesions of rosacea for 16 weeks.</u></li> <li>• <u>To evaluate the safety and tolerability of oral DFD-29 (minocycline HCl 40 mg capsules) in comparison to DFD-29 (minocycline HCl 20 mg capsules) in the treatment of inflammatory lesions of rosacea for 16 weeks.</u></li> </ul>
<p><b>Section 7.1: Study Endpoints</b></p>	<p><b>Co-Primary endpoints:</b></p> <ul style="list-style-type: none"> <li>• Proportion of subjects with IGA (modified scale without erythema) success – Grade 0 or 1 at the end of study with at least 2 grade reduction from Baseline</li> </ul>	<p><b>Endpoints were moved to the Section 8.7: study parameters</b></p>

	<p>to Week 16.</p> <ul style="list-style-type: none"><li>• Total inflammatory lesion count (sum of papules, pustules, and nodules) reduction from Baseline to Week 16.</li></ul> <p><b>Secondary Endpoints</b></p> <ul style="list-style-type: none"><li>• Proportion of subjects with at least a two grade improvement of IGA (modified scale without erythema) grade from Baseline to Week 16.</li><li>• Change in clinician's erythema assessment (CEA) score from Baseline to Week 16.</li><li>• Total inflammatory lesion count reduction from Baseline compared to Weeks 4, 8 and 12.</li><li>• Percentage reduction in total inflammatory lesion count from Baseline to Week 16.</li><li>• Change in Telangiectasia score from Baseline to Week 16.</li></ul> <p><b>Exploratory Endpoints</b></p> <ul style="list-style-type: none"><li>• Mean change in high sensitivity C-reactive protein (hs-CRP) levels from Baseline compared to Week 16.</li><li>• Proportion of subjects meeting CEA treatment success criteria (i.e. a two grade improvement in the CEA scale) at weeks 4, 8, and 12.</li><li>• Proportion of subjects meeting IGA treatment success criteria (i.e. a two grade improvement in the IGA scale) at weeks 4, 8, and 12.</li><li>• Proportion of subjects meeting the CEA treatment success criteria at the end of the study will be compared between placebo, the 10 mg, 20 mg, and 40 mg dose levels of DFD-29.</li><li>• Proportion of subjects meeting the IGA treatment</li></ul>	
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	<p>success criteria at the end of the study will be compared between placebo, the 10 mg, 20 mg, and 40 mg dose levels of DFD-29.</p> <ul style="list-style-type: none"> <li>• Comparison of the above-mentioned efficacy parameters between two dose levels (i.e. 40 mg vs 20 mg, 40 mg vs 10 mg, and 20 mg vs 10 mg) of DFD-29.</li> </ul>	
<p><b>Section 8.1: Overall Design</b></p>	<p>This is a 16-week, multicenter, placebo-controlled, randomized, parallel group, double-blind study. Subjects, who are at least 18 years old, diagnosed with papulopustular rosacea will be randomized to one of the following treatments:</p> <ol style="list-style-type: none"> <li>1. DFD-29 (minocycline HCl) Extended Release Capsules (10 mg) once daily for 16 weeks</li> <li>2. DFD-29 (minocycline HCl) Extended Release Capsules (20 mg) once daily for 16 weeks</li> <li>3. DFD-29 (minocycline HCl) Extended Release Capsules (40 mg) once daily for 16 weeks</li> <li>4. DFD-29 placebo capsules once daily for 16 weeks</li> </ol> <p>...</p>	<p>This is a 16-week, multicenter, <del>placebo</del>-controlled, randomized, parallel group, double-blind study. Subjects, who are at least 18 years old <u>and</u> diagnosed with papulopustular rosacea will be randomized to one of the following treatments:</p> <ol style="list-style-type: none"> <li>1. DFD-29 (minocycline HCl) Extended Release Capsules (40 mg) once daily for 16 weeks</li> <li>2. DFD-29 (minocycline HCl) Extended Release Capsules (20 mg) once daily for 16 weeks</li> <li>3. <del>DFD-29 (minocycline HCl) Extended</del> Oracea<sup>®</sup> (doxycycline) Modified Release Hard Capsules (40 mg) once daily for 16 weeks</li> <li>4. Placebo capsules once daily for 16 weeks</li> </ol> <p>... <u>Impact of the treatment on the Quality of Life (QoL) of the subjects will be done using a rosacea specific tool RosaQoL at Baseline, and at weeks 4, 8, 12 and 16.</u></p>
<p><b>Section 8.1.2.1: Screening (Visit 1)</b></p>	<ul style="list-style-type: none"> <li>• Evaluation of vital sign parameters (refer to Section <a href="#">8.1.3.4</a>)</li> <li>• Physical examination (refer to Section <a href="#">8.1.3.5</a>)</li> <li>• ...</li> <li>• Inclusion and Exclusion Criteria</li> </ul>	<ul style="list-style-type: none"> <li>• Evaluation of vital sign parameters (<del>refer to section</del> <a href="#">Section 8.1.3.4</a>)</li> <li>• Physical examination (<del>refer to section</del> <a href="#">Section 8.1.3.5</a>)</li> <li>• ...</li> <li>• <a href="#">RosaQoL (Section 8.1.4.4)</a></li> <li>• Inclusion and Exclusion Criteria (<a href="#">Sections 8.2.1 and 8.2.2</a>)</li> </ul> <p>Week 2 (Phone call)</p> <ul style="list-style-type: none"> <li>• <a href="#">Eligibility confirmation (based on inclusion (Section 8.2.1) and</a></li> </ul>

		<p><u>exclusion criteria (Section 8.2.2))</u></p> <ul style="list-style-type: none"> <li>• Review of AEs...</li> </ul> <p><u>RosaQoL Score (Section 8.1.4.4) was added to Visit 2, Visit 3, Visit 4, Visit 5 and Visit 6</u></p> <p>In Section 8.1.2.2 Hs CRP was deleted</p>																					
<p><b>Section 8.1.4.4: Rosacea Quality of Life (RosaQoL)</b></p>	<p>...</p>	<p>The RosaQoL assessment is carried out by the Investigator by asking questions as per the validated RosaQoL questionnaire instrument, at every study visit from Screening up to Week 16 (or at early termination). The patients will have to rate on a 5 grade scale their perception of the impact that Rosacea has on various dimensions influencing their quality of life.</p>																					
<p><b>Section 8.2.3.1: Concomitant Medications</b></p>	<p>Drugs that influence the inflammatory lesions in acne and rosacea must be avoided... ...Furthermore, drugs interacting with minocycline or</p> <table border="1" data-bbox="450 863 1133 1391"> <tr> <td data-bbox="450 863 813 927">Other systemic drugs used for treatment of rosacea</td> <td data-bbox="813 863 954 927">30 days</td> <td data-bbox="954 863 1133 927">Prohibited</td> </tr> <tr> <td data-bbox="450 927 813 1114">Antacids containing calcium, magnesium or aluminum, Iron preparations, bismuth subsalicylate</td> <td data-bbox="813 927 954 1114">Not applicable</td> <td data-bbox="954 927 1133 1114">Restricted for 1.5 hours before to 3.0 hours after ingestion of IP</td> </tr> <tr> <td colspan="3" data-bbox="450 1114 1133 1145"><b>Others</b></td> </tr> <tr> <td data-bbox="450 1145 813 1391">Facial procedures such as chemical peel, photodynamic therapy, acne surgery, cryodestruction or chemodestruction, x-ray therapy, intralesional steroids, dermabrasion, or depilation</td> <td data-bbox="813 1145 954 1391">45 days</td> <td data-bbox="954 1145 1133 1391">Prohibited</td> </tr> </table>	Other systemic drugs used for treatment of rosacea	30 days	Prohibited	Antacids containing calcium, magnesium or aluminum, Iron preparations, bismuth subsalicylate	Not applicable	Restricted for 1.5 hours before to 3.0 hours after ingestion of IP	<b>Others</b>			Facial procedures such as chemical peel, photodynamic therapy, acne surgery, cryodestruction or chemodestruction, x-ray therapy, intralesional steroids, dermabrasion, or depilation	45 days	Prohibited	<p>Drugs that influence the inflammatory lesions in acne and rosacea must be avoided. <u>Facial procedures, influencing acne and rosacea [such as chemical peel, photodynamic therapy, acne surgery, cryodestruction or chemodestruction, x-ray therapy, intralesional steroids, dermabrasion, or depilation (except eyebrow shaping), laser therapy or Intense Pulse Light Treatment as well as other procedures on face (Thermage® etc.)] are prohibited from 45 days prior to the intake of study medication throughout the whole study period.</u> <u>Systemic retinoids (including high dose vitamin A &gt;10,000 units per day) must be avoided from 180 days prior to the intake of study medication throughout the whole study period</u> Furthermore, drugs interacting with minocycline <u>and Oracea®</u> or</p> <table border="1" data-bbox="1162 1142 2051 1391"> <tr> <td data-bbox="1162 1142 1682 1206">Systemic retinoid (including high dose vitamin A &gt;10,000 units per day)</td> <td data-bbox="1682 1142 1823 1206">180 days</td> <td data-bbox="1823 1142 2051 1206">Prohibited</td> </tr> <tr> <td data-bbox="1162 1206 1682 1270">Other systemic drugs used for treatment of rosacea</td> <td data-bbox="1682 1206 1823 1270">30 days</td> <td data-bbox="1823 1206 2051 1270">Prohibited</td> </tr> <tr> <td data-bbox="1162 1270 1682 1391">Antacids containing calcium, magnesium or aluminum, Iron preparations, bismuth subsalicylate</td> <td data-bbox="1682 1270 1823 1391">Not applicable</td> <td data-bbox="1823 1270 2051 1391">Restricted for 1.5 hours before to 3.0 hours after ingestion of IP</td> </tr> </table>	Systemic retinoid (including high dose vitamin A >10,000 units per day)	180 days	Prohibited	Other systemic drugs used for treatment of rosacea	30 days	Prohibited	Antacids containing calcium, magnesium or aluminum, Iron preparations, bismuth subsalicylate	Not applicable	Restricted for 1.5 hours before to 3.0 hours after ingestion of IP
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<b>Section 8.2.3.2: Dietary Aspects</b>	Substances which can potentially interfere with absorption of minocycline like antacids containing aluminum	Substances which can potentially interfere with absorption of minocycline like antacids, <u>multivitamins</u> or other <u>products</u> containing aluminum																																																						
<b>Section 8.3: Study Drugs</b>	Study drugs include the investigational product DFD-29 (minocycline HCl) Extended Release Capsules (10 mg, 20 mg, and 40 mg) and matching placebo administered during the study.	Study drugs include the investigational products DFD-29 (minocycline HCl) Extended Release Capsules ( <del>10 mg</del> , 20 mg and 40 mg) <u>and</u> matching placebo <u>and</u> Oraycea® (doxycycline) Modified Release Hard Capsules administered during the study.																																																						
<b>Section 8.3.1: Investigational Product and matching Placebo</b>	Dr. Reddy's will provide DFD-29 (minocycline HCl) Extended Release Capsules (10 mg, 20 mg, and 40 mg) and matching placebo. .....capsules matching DFD-29, formulated with the same	Dr. Reddy's will provide DFD-29 (minocycline HCl) Extended Release Capsules ( <del>10 mg</del> , 20 mg, and 40 mg) and matching placebo. .....capsules matching DFD-29, formulated with the same excipients, but																																																						

	excipients, but without minocycline hydrochloride. The identity of the study drug is given in <a href="#">Table 4</a> . The identity of the placebo is given in <a href="#">Table 5</a> .	without minocycline hydrochloride. <del>The identity of the study drug is given in Table 4. The identity of the placebo is given in Table 5</del> Oraycea <sup>®</sup> capsules are commercially available and will be purchased by ABF. In order to maintain double blinding of all treatments, ‘over-encapsulation’ (enclosing the original capsule within a second larger capsule shell) will be performed. The identity of the study drug is given in <a href="#">Table 4</a> . The identity of the placebo is given in <a href="#">Table 5</a> , the identity of Oraycea <sup>®</sup> is given in <a href="#">Table 6</a> .																						
<b>Section 8.3.1: Investigational Product and matching Placebo</b>	<b>Table 4: Identity of Investigational Medicinal Product</b> Dose strength: 10 mg, 20 mg or 40 mg minocycline	<b>Table 4: Identity of Investigational Medicinal Product</b> Dose strength: <del>10 mg</del> 20 mg or 40 mg minocycline																						
<b>Section 8.3.1: Investigational Product and matching Placebo</b>	No information	<b>Table 6: Identity of Oraycea<sup>®</sup></b> <table border="1"> <thead> <tr> <th></th> <th>Test treatment</th> </tr> </thead> <tbody> <tr> <td>Name:</td> <td>Oraycea<sup>®</sup></td> </tr> <tr> <td>Active ingredient:</td> <td>Doxycycline</td> </tr> <tr> <td>Formulation:</td> <td>Capsule with 30 mg immediate release and 10 mg delayed release beads</td> </tr> <tr> <td>Dose strength:</td> <td>40 mg doxycycline</td> </tr> <tr> <td>Dose:</td> <td>1 capsule</td> </tr> <tr> <td>Posology:</td> <td>1-0-0 (once daily, in the morning)</td> </tr> <tr> <td>Mode of administration:</td> <td>Oral administration with approx. 240 mL water</td> </tr> <tr> <td>Administration condition:</td> <td>Fasting state preferred, but not mandatory</td> </tr> <tr> <td>Duration of administration:</td> <td>16 weeks</td> </tr> <tr> <td>Batch number &amp; Expiry date:</td> <td>Will be given in the TMF ***.</td> </tr> </tbody> </table> <p>*** The documentation allowing traceability will be provided in the TMF.</p>		Test treatment	Name:	Oraycea <sup>®</sup>	Active ingredient:	Doxycycline	Formulation:	Capsule with 30 mg immediate release and 10 mg delayed release beads	Dose strength:	40 mg doxycycline	Dose:	1 capsule	Posology:	1-0-0 (once daily, in the morning)	Mode of administration:	Oral administration with approx. 240 mL water	Administration condition:	Fasting state preferred, but not mandatory	Duration of administration:	16 weeks	Batch number & Expiry date:	Will be given in the TMF ***.
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Batch number & Expiry date:	Will be given in the TMF ***.																							
<b>Section 8.3.2: Study Drug Supply and Packaging</b>	DFD-29 (minocycline HCl) Extended Release Capsules and placebo for DFD-29 will be supplied by Dr. Reddy’s Laboratories as 30 count in HDPE bottle, and the IMPs will be imported and managed by QPS. The qualified	DFD-29 (minocycline HCl) Extended Release Capsules and placebo for DFD-29 will be supplied by Dr. Reddy’s Laboratories as 30 count in HDPE bottle. <del>and the IMPs will be imported and managed by QPS. The qualified person of QPS will certify that the manufacturing and the</del>																						

	<p>person of QPS will certify that the manufacturing and the packaging is carried out in accordance with EU cGMP-guidelines and the IMPD.</p> <p>The study drug will be supplied to QPS where the clinical labeling will be performed. The medication bottles will be labeled according to QPS's procedure</p> <p>... Extended Release Capsules (10 mg, 20 mg and 40 mg) and placebo</p>	<p><del>packaging is carried out in accordance with EU cGMP guidelines and the IMPD.</del></p> <p><u>The study drug will be imported by QPS and further managed by ABF.</u></p> <p><u>The study drugs will be supplied to QPSABF where <del>the over-encapsulation, re-packaging and the clinical labeling</del> will be performed. Over-encapsulation will be performed with DFD-29, placebo and Oraycea<sup>®</sup> capsules in order to achieve double blinding of formulations. Subsequently, the capsules will be re-packed into new HDPE bottles (of specifications identical to the one in which stability of DFD-29 capsules has been evaluated) containing 30 capsules. The medication bottles will be labeled according to QPS'sABF's procedure as stated in Section 8.3.3. <del>A See sample label will be filed in the Investigator File.</del></u></p> <p>... Extended Release Capsules (<del>10 mg</del> 20 mg and 40 mg), <u>Oraycea<sup>®</sup> (doxycycline) Modified Release Hard Capsules</u> and placebo</p>
<b>Section 8.3.3: Study Drug Labeling</b>	<p>The labels will be in German and Dutch language. An English version will be available for review purposes.</p> <ul style="list-style-type: none"> <li>• Study number (DFD-29-CD-002)</li> <li>• Study drug (30x DFD-29 10 mg / 20 mg / 40 mg / placebo Capsules)</li> </ul>	<p>The labels will be in German <del>and Dutch</del> language. An English version will be available for review purposes.</p> <ul style="list-style-type: none"> <li>• Study number (DFD-29-CD-002)</li> <li>• Study drug (30x DFD-29 20 mg / 40 mg / placebo / <u>Oraycea<sup>®</sup> Capsules</u>)</li> </ul>
<b>Section 8.3.3: Study Drug Labeling</b>	<p>Any relabeling activities will be coordinated by QPS Netherlands.</p>	<p>Any relabeling activities will be coordinated by QPS.</p>
<b>Section 8.3.3: Study Drug Labeling</b>	<p>No sample label</p>	<p><u>Bottle Label</u></p>

		<p><u>Prüfplancode: DFD-29-CD-002</u></p> <p><u>EudraCT Nr.: 2016-003197-41</u></p> <p><u>Sponsor: Dr. Reddy's Laboratories Ltd., India; 8-2-337, Road No. 3, Banjara Hills, Hyderabad; Telangana 500034, India; Tel: +91-40-4900 2900</u></p> <p><u>CRO: QPS Austria GmbH; Parkring 12; 8074 Grambach, Austria; Tel.:+43 316 258 111</u></p> <p><u>Inhalt: 30 Kapseln 20 mg Minocyclin oder 40 mg Minocyclin oder 40 mg Oracea oder Placebo zur oralen Anwendung</u></p> <p><u>Nach Anweisung des Prüfarztes anwenden.</u></p> <p><u>Lagerung bei 15 °C -25 °C.</u></p> <p><u>Für Kinder unzugänglich aufbewahren.</u></p> <p><u>Nur zur klinischen Prüfung bestimmt.</u></p> <p><u>Nicht verbrauchte Kapseln und leere Flaschen sind spätestens beim letzten Studienbesuch zurückzugeben.</u></p> <p><u>Ch.-B.: XXXXX</u></p> <p><u>Verwendbar bis: MM/YYYY</u></p> <p><u>Kitnr.: XXXX</u></p> <p><u>Flasche [X] X = 1 oder 2 oder 3 oder 4 oder Reserve</u></p> <p><u>Patientennr.: _____</u></p> <p><u>Figure 2-1: Sample Label</u></p>
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<b>Section 8.3.6: Storage and Return of Study Drug</b>	All unused investigational material (drugs and packaging) must be returned to QPS.	All unused investigational material (drugs and packaging) must be returned to <u>ABF</u> .
<b>Section 8.6.1: Assignment of Subject Numbers</b>	Subjects will receive a number on Day 1 before start of procedures/assessments. The assignment of number and code for subject identification is based on the obligation for anonymity. The number will consist of a 2-digit site number followed by a 2-digit number. Example: Subject 6 at site 3 will receive subject number 0306.	Subjects will receive a number on Day 1 before start of procedures/assessments. The assignment of number and code for subject identification is based on the obligation for anonymity. <del>The number will consist of a 2-digit site number followed by a 2-digit number. Example: Subject 6 at site 3 will receive subject number 0306.</del> <u>During Screening, the sites will assign three-digit sequential subject numbers preceded by a site number. Upon inclusion into the study, the subjects will receive a four-digit randomization number (kit code) which does not contain site identification.</u>
<b>Section 8.6.2: Treatment Assignment</b>	Subjects will be randomized to any of the treatments assigned in a 1:1:1:1 fashion. Block size will be determined by the statistician of QPS Netherlands. Randomization will be stratified per site.	Subjects will be randomized to any of the treatments assigned in a 1:1:1:1 fashion. Block size will be determined by the statistician of QPS Netherlands. Randomization will be stratified per site <u>and per IGA score (score above or equal to 2) at Baseline. In order to achieve a patient population in the study with adequate representation of patients with moderate to severe illness (IGA score above 2) not more than 20 % of enrollments in the study will be of IGA grade 2 at Baseline.</u>
<b>Section 8.6.3: Double-blinding</b>	The investigational product and its matching placebo are indistinguishable	The investigational product and its matching placebo <u>and active comparator (Oraycea<sup>®</sup>) are indistinguishable after over-encapsulation</u>
<b>Section 8.6.4: Emergency Procedure for Unblinding</b>	...access to digital emergency envelopes.  Investigators are immediately notified by the Sealed Envelope™ in case of unblinding. Documentation about any code break must be documented and attached to the eCRF.	...access to <del>digital</del> emergency envelopes.  <del>Investigators are immediately notified by the Sealed Envelope™ in case of unblinding.</del> Documentation about any code break must be documented and attached to the eCRF.

<p><b>Section</b> 8.7.1: <b>Efficacy Parameters Endpoints</b></p>	<p><b>Co-Primary endpoints:</b></p> <ul style="list-style-type: none"> <li>Proportion of subjects with IGA (modified scale without erythema) success – Grade 0 or 1 at the end of study with at least 2 grade reduction from Baseline to Week 16.</li> </ul> <p>Total inflammatory lesion count (sum of papules, pustules, and nodules) reduction from Baseline to Week 16.</p> <p><b>Secondary endpoints</b></p> <ul style="list-style-type: none"> <li>Proportion of subjects with at least a two grade improvement of IGA (modified scale without erythema) grade from Baseline to Week 16.</li> <li>Change in clinician’s erythema assessment (CEA) score from Baseline to Week 16.</li> <li>Total inflammatory lesion count reduction from Baseline compared to Weeks 4, 8 and 12.</li> <li>Percentage reduction in total inflammatory lesion count from Baseline to Week 16.</li> </ul> <p>Change in Telangiectasia score from Baseline to Week 16.</p> <p><b>Exploratory Endpoints</b></p> <ul style="list-style-type: none"> <li>Mean change in high sensitivity C-reactive protein (hs-CRP) levels from Baseline compared to Week 16.</li> <li>Proportion of subjects meeting CEA treatment success criteria (i.e. a two grade improvement in the CEA scale) at weeks 4, 8, and 12.</li> <li>Proportion of subjects meeting IGA treatment success criteria (i.e. a two grade improvement in the IGA scale) at weeks 4, 8, and 12.</li> <li>Proportion of subjects meeting the CEA treatment</li> </ul>	<p><b>Co-Primary Endpoints:</b></p> <ul style="list-style-type: none"> <li>Proportion of subjects with IGA (modified scale without erythema) <del>success</del> <u>‘treatment success’</u> – Grade 0 or 1 at the end of study with at least 2 grade reduction from Baseline to Week 16.</li> <li>Total inflammatory lesion count (sum of papules, pustules, and nodules) reduction from Baseline to Week 16.</li> </ul> <p><b>Secondary Endpoints</b></p> <ul style="list-style-type: none"> <li>Proportion of subjects with at least a <del>two</del> 2 grade <del>improvement</del> <u>reduction in of IGA (modified scale without erythema) grade</u> <del>‘treatment success’</del> <u>score</u> from Baseline to Week 16.</li> <li><del>Change in clinician’s erythema assessment (CEA) score from Baseline to Week 16.</del></li> <li><del>Total inflammatory lesion count reduction from Baseline compared to Weeks 4, 8 and 12.</del></li> <li><del>Percentage reduction – Median change in total inflammatory lesion count from Baseline to Week 16.</del></li> </ul> <p><u>Change in Telangiectasia RosaQoL score from Baseline to Week 16</u></p> <p><b>Exploratory Endpoints</b></p> <ul style="list-style-type: none"> <li><u>Proportion of subjects with IGA (modified scale without erythema) ‘treatment success’ from Baseline to Weeks 4, 8 and 12.</u></li> <li><u>Total inflammatory lesion count (sum of papules, pustules, and nodules) reduction from Baseline to Weeks 4, 8 and 12.</u></li> <li><u>Proportion of subjects with at least a 2 grade reduction in IGA (modified scale without erythema) score from baseline to week 4, 8 and 12.</u></li> <li><u>Median change in total RosaQoL score from Baseline to Weeks 4, 8 and 12.</u></li> <li>Mean change in high sensitivity C-reactive protein (hs-CRP) levels from Baseline compared to Week 16.</li> <li><u>Change in Telangiectasia score from Baseline compared to Week 16.</u></li> </ul>
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	<p>success criteria at the end of the study will be compared between placebo, the 10 mg, 20 mg, and 40 mg dose levels of DFD-29.</p> <ul style="list-style-type: none"> <li>Proportion of subjects meeting the IGA treatment success criteria at the end of the study will be compared between placebo, the 10 mg, 20 mg, and 40 mg dose levels of DFD-29.</li> </ul> <p>Comparison of the above-mentioned efficacy parameters between two dose levels (i.e. 40 mg vs 20 mg, 40 mg vs 10 mg, and 20 mg vs 10 mg) of DFD-29.</p>	<ul style="list-style-type: none"> <li>Proportion of subjects meeting CEA ‘treatment success’ criteria (i.e. a two grade improvement in the CEA scale) at weeks 4, 8, 12 <u>and 16</u>.</li> <li><del>Proportion of subjects meeting IGA treatment success criteria (i.e. a two grade improvement in the IGA scale) at weeks 4, 8, and 12.</del></li> <li><del>Proportion of subjects meeting the CEA treatment success criteria at the end of the study will be compared between placebo, the 10 mg, 20 mg, and 40 mg dose levels of DFD-29.</del></li> <li><del>Proportion of subjects meeting the IGA treatment success criteria at the end of the study will be compared between placebo, the 10 mg, 20 mg, and 40 mg dose levels of DFD-29.</del></li> <li>Comparison of the above-mentioned efficacy parameters between two dose levels (i.e. 40 mg vs 20 mg, 40 mg vs 10 mg, and 20 mg vs 10 mg) of DFD-29.</li> </ul>
<p><b>Section 8.7.2: Safety and Tolerability Parameters Endpoints</b></p>	<ul style="list-style-type: none"> <li>Change from baseline to each scheduled time point up to EOS for vital signs compared between DFD-29 and placebo.</li> <li>Change from Screening up to EOS for physical examination compared between DFD-29 and placebo.</li> <li>Change from Screening up to EOS for clinical laboratory tests compared between DFD-29 and placebo.</li> <li>Treatment-emergent AEs up to EOS compared between DFD-29 and placebo.</li> <li>Treatment-emergent AEs leading to premature discontinuation of study drug compared between DFD-29 and placebo.</li> <li>Treatment-emergent SAEs up to EOS compared between DFD-29 and placebo.</li> </ul>	<ul style="list-style-type: none"> <li>Change from Baseline to each scheduled time point up to EOS for vital signs <del>compared between DFD-29 and placebo.</del></li> <li>Change from Screening up to EOS for physical examination <del>compared between DFD-29 and placebo.</del></li> <li>Change from Screening up to EOS for clinical laboratory tests <del>compared between DFD-29 and placebo.</del></li> <li>Treatment-emergent AEs up to EOS <del>compared between DFD-29 and placebo.</del></li> <li>Treatment-emergent AEs leading to premature discontinuation of study drug <del>compared between DFD-29 and placebo.</del></li> <li>Treatment-emergent SAEs up to EOS <del>compared between DFD-29 and placebo.</del></li> </ul>
<p><b>Section 9.1.3: Relationship to Study Drug</b></p>	<p>...causal relationship to the study drug and reported as either definite, probable, possible, unlikely, not related, not assessable as defined in Table 6:.</p>	<p>...causal relationship to the study drug and reported as either definite, probable, possible, <del>unlikely</del>, not related, <del>not assessable</del> as defined in <del>Table 6:</del> <u>below:</u></p>

**Table 6: Causality Categories**

Causality Term	Assessment definition
<b>DEFINITE</b>	<ul style="list-style-type: none"> <li>Definite temporal relationship with drug treatment.</li> <li>Known or suspected reaction to the administered investigational study medication.</li> <li>Improvement on stopping of dosage, reappearance of reaction on re-exposure.</li> <li>Event cannot be explained by subject's clinical state or other factors.</li> </ul>
<b>PROBABLE</b>	<ul style="list-style-type: none"> <li>Reasonable temporal sequence with drug administration.</li> <li>Likely to be known reaction to the administered investigational study medication.</li> <li>Event cannot easily be explained by subject's clinical state or other factors.</li> </ul>
<b>POSSIBLE</b>	<ul style="list-style-type: none"> <li>Reasonable temporal relationship with drug treatment.</li> <li>Event could have also been caused by subject's clinical state.</li> </ul>
<b>UNLIKELY</b>	<ul style="list-style-type: none"> <li>Poor or no temporal relationship with drug treatment.</li> </ul>

**Table 6: Causality Categories**

Causality Term	Assessment definition
<b>DEFINITE</b>	<ul style="list-style-type: none"> <li><del>Definite temporal relationship with drug treatment.</del></li> <li><del>Known or suspected reaction to the administered investigational study medication.</del></li> <li><del>Improvement on stopping of dosage, reappearance of reaction on re-exposure.</del></li> <li><del>Event cannot be explained by subject's clinical state or other factors.</del></li> </ul>
<b>PROBABLE</b>	<ul style="list-style-type: none"> <li><del>Reasonable temporal sequence with drug administration.</del></li> <li><del>Likely to be known reaction to the administered investigational study medication.</del></li> <li><del>Event cannot easily be explained by subject's clinical state or other factors.</del></li> </ul>
<b>POSSIBLE</b>	<ul style="list-style-type: none"> <li><del>Reasonable temporal relationship with drug treatment.</del></li> <li><del>Event could have also been caused by subject's clinical state.</del></li> </ul>
<b>UNLIKELY</b>	<ul style="list-style-type: none"> <li><del>Poor or no temporal relationship with drug treatment.</del></li> <li><del>Event can easily also be explained by subject's clinical state or other factors.</del></li> </ul>
<b>NOT RELATED</b>	<ul style="list-style-type: none"> <li><del>No temporal relationship with study drug administration (e.g. Event occurred before dosing).</del></li> <li><del>Event is clearly related to other factors than drug treatment, such as clinical state, concomitant medication or therapeutic intervention.</del></li> </ul>

		<ul style="list-style-type: none"> <li>Event can easily also be explained by subject's clinical state or other factors.</li> </ul>	<p><b>NOT ASSESSABLE</b></p>	<ul style="list-style-type: none"> <li><del>There is not enough data available for an evaluation.</del></li> <li><del>Should only be chosen when all measures have been taken and all attempts have been made without success to obtain enough data for an evaluation. It is not available for the final assessment.</del></li> </ul>
<p><b>NOT RELATED</b></p>	<ul style="list-style-type: none"> <li>No temporal relationship with study drug administration (e.g. Event occurred before dosing).</li> <li>Event is clearly related to other factors than drug treatment, such as clinical state, concomitant medication or therapeutic intervention.</li> </ul>			
<p><b>NOT ASSESSABLE</b></p>	<ul style="list-style-type: none"> <li>There is not enough data available for an evaluation.</li> <li>Should only be chosen when all measures have been taken and all attempts have been made without success to obtain enough data for an evaluation. It is not available for the final assessment.</li> </ul>			
<ol style="list-style-type: none"> <li><u>Not Related: The event is clearly due to extraneous causes (e.g., diseases, environment, etc.). Specify if known. Or, the event is most probably produced by other factors such as the subject's clinical state, therapeutic interventions, or concomitant therapy and does not follow a known response pattern to the study product.</u></li> <li><u>Possibly Related: The event is temporally related to study product use but can be explained by another etiology. Information on the effect of study product withdrawal may be lacking.</u></li> <li><u>Probably Related: The event is temporally related to study product use and is consistent with known effects of the study product and/or improves upon withdrawal of the study product.</u></li> <li><u>Definitely Related: The event follows a reasonable temporal sequence from the time of study product administration and/or follows a known response pattern to the study product, and could not have been produced by other factors such as the subject's clinical state, therapeutic intervention, or concomitant therapy, and either occurs immediately following study product administration or improves on stopping the product, or there is a positive reaction at the application site.</u></li> </ol>				

<p><b>10.2: Analysis Sets Populations</b></p>	<p>... analysis population as described below.</p> <p><b>All-treated set:</b> This analysis set includes all randomized subjects who received study drug (at least one dose).</p> <p><b>Intention to treat set:</b> This analysis set includes all subjects who have received one or more doses and have undergone at least one post-baseline efficacy evaluation.</p> <p><b>Safety set:</b> This analysis set includes subjects from the all-treated set who had at least one safety assessment post-baseline. The safety set will be employed in the analysis of tolerability and safety variables.</p> <p><b>Per-protocol set:</b> This analysis set comprises all subjects included in the All-treated set who did not violate the protocol in a way that might affect the evaluation of the effect of the study drug(s) on the primary endpoint, i.e., without major protocol violations or deviations.</p>	<p>... analysis population as described below.</p> <p><del>All-treated set:</del> This analysis set includes all randomized subjects who received study drug (at least one dose).</p> <p><b>Intention to treat setpopulation:</b> This analysis setpopulation includes all subjects who have <del>received one or more doses been randomized and have undergone at least one post-baseline efficacy evaluation</del>dispensed the study drug.</p> <p><b>Safety setpopulation:</b> This analysis setpopulation includes subjects <del>from the all-treated set</del> who had at least one safety assessment post-baseline. The safety setpopulation will be employed in the analysis of tolerability and safety variables.</p> <p><b>Per-protocol setpopulation:</b> This analysis setpopulation comprises all subjects <del>included in the All-treated set</del> who did not violate the protocol in a way that might affect the evaluation of the effect of the study drug(s) on the primary endpoint, i.e., without major protocol violations or deviations.</p>
<p><b>10.2.1: Sample Size</b></p>	<p>missing</p>	<p><u>The above determined sample size of 44 subjects per treatment group was also seen to ensure an adequately powered analysis (87%) for demonstrating non-inferiority of DFD-29 40 mg and DFD-29 20 mg treatments against the active comparator Oraycea<sup>®</sup> while assuming the lower limit of the 90% CI for concluding non-inferiority to be ≤3 for the absolute change in total inflammatory lesion count from baseline at Week 16 for the individual DFD-29 treatment arms versus Oraycea<sup>®</sup> arm, a common standard deviation of 5 lesion counts, the expected difference of treatment means to be 0 and alpha of 0.05 (one sided). Similarly, this sample size will also</u></p>

		<p><u>achieve 91% power to detect a non-inferiority margin difference of 0.5 points on the RosaQoL, assuming a common standard deviation of 0.77 points.</u></p>
<p><b>Section 10.3.1: Statistical Analysis of Efficacy Parameters</b></p>	<p><b>Efficacy</b> Co-Primary endpoints:</p> <ul style="list-style-type: none"> <li>The proportion of subjects with IGA (modified scale without erythema) success – will be investigated with a Chi-square test for placebo versus active treatment. Success is described as having at least 2 grade reduction from baseline with grade 0 or 1 at the end of the study.</li> <li>The difference between placebo and active treatment will be tested for the total inflammatory lesion count reduction from baseline at week 16 with a MIXED Model, with the investigator as a random factor.</li> </ul> <p>Secondary endpoints:</p> <ul style="list-style-type: none"> <li>Proportion of subjects with at least a two grade improvement of IGA (modified scale without erythema) grade from Baseline to Week 16 will be investigated with a Chi-square test comparing placebo with active treatment.</li> <li>Change in clinician’s erythema assessment (CEA) score from Baseline to Week 16 will be investigated with an ANOVA comparing placebo with active treatment.</li> <li>The difference between placebo and active treatment will be tested for the total inflammatory lesion count reduction from Baseline, at Weeks 4, 8 and 12 using MIXED Model with the investigator as a random factor.</li> </ul>	<p><b>Efficacy</b> <u>For all endpoints, the comparison of oral DFD-29 (40 mg capsule) versus placebo will be the primary objective of the study. All other comparisons viz , between oral DFD-29 (20 mg capsule) and placebo, between oral DFD-29 (40 and 20 mg capsules) and Oraycea® and between oral DFD-29 40 mg capsules and DFD-29 20 mg capsules, will be treated as secondary.</u></p> <p><del>Co-Primary endpoints</del><b>Endpoints:</b></p> <ul style="list-style-type: none"> <li>The proportion of subjects with IGA (modified scale without erythema) <u>treatment</u> success – will be investigated with a Chi-square test <del>for placebo versus active treatment.</del> <u>Treatment</u> Success is described as having at least 2 grade reduction from baseline with grade 0 or 1 at <del>the end of the study</del> <u>Week 16.</u></li> <li>The difference between <del>placebo and active treatment</del> <u>will be tested for the treatments in terms of the change from baseline in the total inflammatory lesion count reduction from baseline at Week 16</u> <del>with a</del> <u>will be tested using MIXED Model,</u> with the investigator as a random factor.</li> </ul> <p><del>Secondary endpoints</del><b>Endpoints:</b></p> <ul style="list-style-type: none"> <li><u>The proportion of subjects with at least a 2 grade reduction in IGA (modified scale without erythema) score from baseline to week 16, will be investigated with a Chi-square test.</u></li> <li><u>Median change in total RosaQoL score from Baseline to Week 16 will be analyzed using ANOVA.</u></li> <li><u>For secondary and exploratory endpoints we assume that non-inferiority would be established if the mean change in inflammatory</u></li> </ul>

	<ul style="list-style-type: none"> <li>• Percentage reduction in total inflammatory lesion count from Baseline to Week 16 will be investigated.</li> <li>• Change in Telangiectasia score from Baseline to Week 16 will be investigated with an ANOVA comparing placebo with active treatment.</li> </ul>	<p><del>lesion count reduction from Baseline, at Weeks 4, 8 and 12 using MIXED Model with the investigator as a random factor.</del></p> <ul style="list-style-type: none"> <li>• <del>Percentage reduction in total inflammatory lesion count from Baseline to Week 16 will be investigated.</del></li> <li>• <del>Change in Telangiectasia score from Baseline to Week 16 will be investigated with an ANOVA comparing placebo with active treatment.</del></li> <li>• <del>Exploratory endpoints:</del></li> <li>• <del>The difference between placebo and active treatment will be tested for the mean change in high sensitivity C reactive protein (hs-CRP) levels from Baseline to Week 16 using ANOVA.</del></li> <li>• <del>The proportion of subjects meeting the CEA treatment success criteria at Weeks 4, 8, and 12 for placebo versus active treatment will be tested using a Chi-square test.</del></li> <li>• <del>The proportion of subjects meeting in the IGA treatment success criteria at Weeks 4, 8, and 12 for placebo versus active treatment will be tested using a Chi-square test.</del></li> <li>• <del>The proportion of subjects meeting DFD-29 (40 mg capsule) group would be within 3 less than in the treatment success criteria in terms of CEA at Oraycea<sup>®</sup> group for the end lower limit of the study will be compared between the 10 mg, 20 mg, and 40 mg dose levels of DFD-29 using a Chi-square test.</del></li> <li>• <del>The proportion of subjects meeting the treatment success criteria in terms of IGA at the end of the study will be compared between the 10 mg, 20 mg, and 40 mg dose levels of DFD-29 using a Chi-square test.</del></li> <li>• <del>Comparison of the above mentioned exploratory efficacy parameters of the differences between two dose levels (i.e. 40 mg vs 20 mg, 40 mg vs 10 mg, and 20 mg vs 10 mg) of DFD-29 using ANOVA 90% Confidence Intervals</del></li> </ul>
<p><b>10.4</b></p>	<p>Safety set is used to perform all safety analyses. most recent MedDRA version</p>	<p>Safety <del>set</del> <u>population</u> is used to perform all safety analyses. ...most recent MedDRA version <u>at the study start.</u></p>

	<p>...observations, and change from screening or baseline. Individual subject listings of vital signs data and laboratory measurements will be provided.</p>	<p>...observations, and change from screening or baseline <u>for the following parameters:</u></p> <ul style="list-style-type: none"> <li>• <u>Change from Baseline to each scheduled time point up to EOS for vital signs compared between DFD-29, Oraycea<sup>®</sup> and placebo.</u></li> <li>• <u>Change from Screening up to EOS for physical examination compared between DFD-29, Oraycea<sup>®</sup> and placebo.</u></li> <li>• <u>Change from Screening up to EOS for clinical laboratory tests compared between DFD-29 Oraycea<sup>®</sup> and placebo.</u></li> <li>• <u>Treatment-emergent AEs up to EOS compared between DFD-29, Oraycea<sup>®</sup> and placebo.</u></li> <li>• <u>Treatment-emergent AEs leading to premature discontinuation of study drug compared between DFD-29, Oraycea<sup>®</sup> and placebo.</u></li> <li>• <u>Treatment-emergent SAEs up to EOS compared between DFD-29, Oraycea<sup>®</sup> and placebo.</u></li> </ul>
<p><b>Section 10.7: Exploratory Analysis</b></p>	<p>Exploratory analyses for the following subgroups will be performed:</p> <ul style="list-style-type: none"> <li>• Male versus female.</li> <li>• Moderate (score 2) and severe (score 3 and 4) IGA score.</li> <li>• Normal hs-CRP versus abnormal hs-CRP at baseline.</li> </ul> <p>Exploratory Endpoints:</p> <ul style="list-style-type: none"> <li>• The difference between placebo and active treatment will be tested for the mean change in high sensitivity C-reactive protein (hs-CRP) levels from baseline at Weeks 8 and 16 using ANOVA.</li> <li>• The proportion of subjects meeting the</li> </ul>	<p><del>Exploratory analyses for the following subgroups will be performed:</del></p> <ul style="list-style-type: none"> <li>• <del>Male versus female.</del></li> <li>• <del>Moderate (score 2) and severe (score 3 and 4) IGA score.</del></li> <li>• <del>Normal hs-CRP versus abnormal hs-CRP at baseline.</del></li> </ul> <p>Exploratory Endpoints:</p> <ul style="list-style-type: none"> <li>• <u>The difference between placebo and active treatment <u>Proportion of subjects with at least a two grade improvement of IGA (modified scale without erythema) grade from Baseline to Weeks 4, 8 and 12 will be investigated with a Chi-square test.</u></u></li> <li>• <u>The difference between treatments in terms of the change from baseline in the total inflammatory lesion count at Weeks 4, 8 and 12 will be tested using MIXED Model with the investigator as a random factor.</u></li> <li>• <u>The proportion of subjects with at least a 2 grade reduction in</u></li> </ul>

	<p>Treatment success criteria (in terms of IGA and CEA) at weeks 4, 8, 12 and 16 for each active treatment versus placebo will be tested using a Chi-square test.</p> <ul style="list-style-type: none"> <li>The proportion of subjects meeting the Treatment success criteria (in terms of IGA and CEA) at the end of the study will be compared between the 10 mg, 20 mg, and 40 mg dose levels of DFD-29..</li> </ul>	<p><u>IGA (modified scale without erythema) score from baseline to week 4, 8 and 12, will be investigated with a Chi-square test.</u></p> <ul style="list-style-type: none"> <li><u>Median change in total RosaQol score from baseline to Weeks 4, 8 and 12 will be investigated using ANOVA.</u></li> <li><u>The difference between treatments will be tested for the mean change in high sensitivity C-reactive protein (hs-CRP) levels from baseline at Weeks 8 and Baseline to Week 16 using ANOVA</u></li> <li><u>The proportion Change in Telangiectasia score from Baseline to Week 16 will be investigated using ANOVA.</u></li> <li><u>Proportion of subjects meeting the Treatment success CEA 'treatment success' criteria (in terms of IGA and CEA) at weeks 4, 8, 12 and 16 for each active i.e. a two grade improvement in the CEA scale) in the treatment versus placebo groups at Weeks 4, 8, 12 and 16 will be tested investigated using a Chi-square test ANOVA.</u></li> </ul> <p><del>The proportion of subjects meeting the Treatment success criteria (in terms of</del></p> <p><u>Exploratory analyses for the following subgroups will be performed:</u></p> <ul style="list-style-type: none"> <li>Male versus female.</li> <li><del>IGA and CEA) at the end of the study will be compared between the 10 mg, 20 mg, and 40 mg dose levels of DFD-29.</del></li> <li><u>Mild (score 2), moderate (score 3) and severe (score 4) IGA score.</u></li> <li><u>Normal hs-CRP versus abnormal hs-CRP at baseline</u></li> </ul>
<p><b>Section 11.1.6: Handling of Study Drug</b></p>	<p>QPS will supply all study drug...</p>	<p><u>ABF</u> will supply all study drug...</p>

<b>Appendix: Section 13.1: IGA</b>	<b>Table 1: IGA Scale</b>	<b>Table 1: IGA Scale</b>																																			
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		2.5 <u>Example of the Rosacea Quality of Life Instrument</u>																																			

### 3 TABLE OF CONTENTS

1	Signature Page .....	4
2	Signature Page for Investigator.....	5
	<b>PROTOCOL CHANGES LOG .....</b>	<b>6</b>
2.5	Example of the Rosacea Quality of Life Instrument.....	42
3	Table of Contents.....	43
4	List of Abbreviations .....	47
5	Protocol Synopsis .....	49
6	Introduction and Rationale.....	58
6.1	Introduction .....	58
6.2	Study Rationale .....	59
6.2.1	Dose Selection .....	60
6.2.2	Ethical Conduct of the Study .....	60
7	Study Objectives .....	61
8	Study Design.....	62
8.1	Overall Study Design .....	62
8.1.1	Informed Consent.....	62
8.1.2	Baseline Parameters and Concomitant Medications.....	63
8.1.2.1	Screening (Visit 1).....	63
8.1.2.2	Baseline (Visit 2).....	63
8.1.2.3	Prior and Concomitant Medications .....	63
8.1.3	Safety and Tolerability Assessments .....	64
8.1.3.1	Activities scheduled at Individual Study Visits.....	64
8.1.3.2	Adverse Events .....	66
8.1.3.3	Telephonic Enquiry .....	66
8.1.3.4	Vital Signs .....	66
8.1.3.5	Physical Examination .....	66
8.1.3.6	Weight and Height.....	66
8.1.3.7	Laboratory Assessments .....	67
8.1.4	Efficacy Assessments.....	67
8.1.4.1	Investigator’s Global Assessment (IGA).....	67
8.1.4.2	Total Inflammatory Lesion Count .....	67
8.1.4.3	Clinician’s Erythema Assessment (CEA).....	67
8.1.4.4	Rosacea Quality of Life (RosaQoL).....	68
8.1.4.5	High sensitive C-reactive Protein (hs-CRP).....	68
8.1.4.6	Telangiectasia Score .....	68
8.1.5	Pregnancy test .....	68
8.2	Study Population .....	68
8.2.1	Inclusion Criteria .....	68
8.2.2	Exclusion Criteria .....	69
8.2.3	Diet, Activities, and Other Restrictions .....	71

8.2.3.1	Concomitant Medication .....	71
8.2.3.2	Dietary Aspects.....	72
8.2.3.3	Sun Exposure.....	72
8.2.3.4	Contraceptives .....	72
8.3	Study Drugs.....	72
8.3.1	Investigational Product and Matching Comparators.....	72
8.3.2	Study Drug Supply and Packaging .....	74
8.3.3	Study Drug Labeling.....	76
8.3.4	Study Drug Administration.....	78
8.3.5	Drug Accountability.....	78
8.3.6	Storage and Return of Study Drug.....	78
8.4	Study Drug Discontinuation and Study Withdrawal.....	78
8.4.1	Study Drug Interruption or Discontinuation .....	78
8.4.2	Study Discontinuation.....	79
8.4.3	Subject’s Follow-up after Study Discontinuation.....	80
8.5	Treatment Exposure and Compliance .....	80
8.6	Treatment Assignment and Blinding.....	81
8.6.1	Assignment of Subject Numbers .....	81
8.6.2	Treatment Assignment.....	81
8.6.3	Double-blinding .....	81
8.6.4	Emergency Procedure for Unblinding .....	82
8.7	Study Parameters.....	82
8.7.1	Efficacy Endpoints.....	82
8.7.2	Safety and Tolerability Endpoints .....	83
9	Safety Definitions and Reporting Requirements .....	84
9.1	Adverse Events.....	84
9.1.1	Definitions of Adverse Events .....	84
9.1.2	Intensity of Adverse Events .....	85
9.1.3	Relationship to Study Drug.....	85
9.1.4	Reporting of Adverse Events .....	86
9.1.5	Follow-up of Adverse Events .....	86
9.2	Serious Adverse Events.....	86
9.2.1	Definitions.....	86
9.2.1.1	Serious Adverse Events .....	86
9.2.1.2	Hospitalization - Prolongation of Existing Hospitalization.....	87
9.2.1.3	Serious Adverse Events Related to Study-mandated Procedures.....	87
9.2.2	Reporting of Serious Adverse Events .....	87
9.2.2.1	Before Study Drug Initiation .....	87
9.2.2.2	During Study Drug Administration .....	87
9.2.2.3	After Study Drug Discontinuation.....	88
9.2.2.4	Reporting Procedures .....	88
9.2.1	Follow-up of Serious Adverse Events .....	89
9.3	Pregnancies.....	90
10	Statistical Methodology and Analyses.....	91

10.1	Statistical Analysis Plan	91
10.2	Analysis Populations	91
10.2.1	Sample Size	91
10.2.2	Handling of Missing Data	92
10.3	Efficacy Parameters	92
10.3.1	Statistical Analysis of Efficacy Parameters	92
10.4	Safety and Tolerability Parameters	93
10.5	Exposure to Study Drugs	94
10.6	Baseline Parameters and Concomitant Medications	94
10.7	Exploratory Analyses	94
10.8	Clinical Study Report	95
11	Procedures and Good Clinical Practice	96
11.1	Procedures	96
11.1.1	Protocol Amendments	96
11.1.1.1	Non-substantial Amendment	96
11.1.1.2	Substantial Amendment	96
11.1.1.3	Urgent Amendment	96
11.1.2	Monitoring	97
11.1.3	Data management	97
11.1.3.1	Data Collection	97
11.1.3.2	Database Management and Quality Control	98
11.1.4	Recording of Data and Retention of Documents	98
11.1.5	Audit	98
11.1.6	Handling of Study Drugs	99
11.1.7	Publication of Study Results	99
11.1.8	Disclosure and Confidentiality	99
11.1.9	Premature Termination or Suspension of the Study	99
11.2	Good Clinical Practice	100
11.2.1	Ethics and Good Clinical Practice	100
11.2.2	Ethics Committee / Institutional Review Board	100
11.2.3	Informed Consent	100
11.2.4	Compensation to Subjects and Investigators	100
12	Structured Risk Analysis	101
13	References	102
14	Appendices	105
14.1	IGA	105
14.2	CEA	105
14.3	Telangiectasia Score	105
14.4	Diagram of the Face	106
14.5	Example of the Rosacea Quality of Life Instrument	107

**List of figures**

Figure 8-1: Flowchart for dispensing and returning of study medication .....	75
Figure 8-2: Sample Label.....	77
Figure 13-1: Diagram of the Face .....	106
Figure 13-2: Example of the Rosacea Quality of Life Instrument.....	107

**List of tables**

Table 1: Visit and Assessment Schedule .....	57
Table 2: Summary of Clinical Laboratory Tests.....	67
Table 3: Prohibited Topical Drugs, Systemic Drugs, and Other Treatments .....	71
Table 4: Identity of Investigational Medical Products.....	73
Table 5: Identity of Placebo .....	73
Table 6: Identity of Oraycea <sup>®</sup> .....	73
Table 7: Efficacy of Oracea <sup>®*</sup> 40 mg/day as shown in two phase 3 trials.....	92
Table 8: IGA Scale.....	105
Table 9: CEA Scale.....	105
Table 10: Telangiectasia Score .....	105

#### 4 LIST OF ABBREVIATIONS

AE	Adverse Event
ALT (SGPT)	Alanine aminotransferase
ANOVA	Analysis of Variance
ATC	Anatomical Therapeutic Chemical (ATC) Classification System
BP	Blood Pressure
bpm	Beats per minute
BPO	Benzoyl Peroxide
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CEA	Clinician's Erythema Assessment
cGMP	Current Good Manufacturing Practice
CI	Confidence Interval
CRA	Clinical Research Associate
CRO	Contract Research Organization
CRP	C-reactive Protein
CRS	Clinical Research Services
DFD-29	Minocycline HCl (formulated as Extended Release Capsules)
eCRF	Electronic Case Report Form
EC	Ethic Committee
EDC	Electronic Data Capture
EOS	End of Study
FAS	Full analysis set
GCP	Good Clinical Practice
HbsAG	Hepatitis B surface antigen
HCl	Hydrochloride
HCV	Hepatitis C Virus
HDPE	High-density polyethylene
HIV	Human immunodeficiency virus
hCG	Human chorionic gonadotropin
hs-CRP	high sensitivity C-reactive protein
ICH	International Conference on Harmonization
IGA	Investigator's Global Assessment modified scale without erythema
ITT	Intention to treat
IRB	Institutional Review Board
IUD	Intra-Uterine Device
IUS	Intra-Uterine Hormone Releasing System
kg	Kilogram
LDH	Lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Affairs
mg	Milligram
MI	Multiple Imputation
mIU	Milli International Units
mL	Milliliter

OTC	Over The Counter
PHY	Phymatous rosacea
PP	Per protocol
PPR	Papulopustular rosacea
QA	Quality Assurance
QP	Qualified Person
QoL	Quality of Life
RosaQoL	Rosacea Quality of Life
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOC	System Organ Class
SOP	Standard Operating Procedure
SUSAR	Suspected Unexpected Serious Adverse Reactions
TLR	Toll-like receptors
TMF	Trial Master File
UV	Ultraviolet
USFDA	United States Food and Drug Administration
WHO	World Health Organization

## 5 PROTOCOL SYNOPSIS

TITLE	A Multi-Center, Randomized, Double-Blind, Parallel-Group, Controlled Study to Assess the Efficacy, Safety and Tolerability of Oral DFD-29 Extended Release Capsules for the Treatment of Inflammatory Lesions of Rosacea over 16 weeks
PHASE	2
CENTERS / COUNTRIES	At least 15 centers in Germany
INVESTIGATIONAL PRODUCT and DOSAGE FORMS	DFD-29 (minocycline HCl) Extended Release Capsules containing minocycline hydrochloride equivalent to 20 mg, and 40 mg of minocycline.
COMPARATIVE PRODUCT and DOSAGE FORMS	Placebo capsules Oraycea <sup>®</sup> modified release hard capsules containing 40 mg of anhydrous doxycycline
ROUTE OF ADMINISTRATION	Oral administration
OBJECTIVES	<p><b>Primary Objectives:</b></p> <ul style="list-style-type: none"> <li>To evaluate the efficacy of oral DFD-29 (minocycline HCl 40 mg capsules) in comparison to placebo in the treatment of inflammatory lesions of rosacea for 16 weeks</li> <li>To evaluate the safety and tolerability of oral DFD-29 (minocycline HCl 40 mg capsules) in comparison to placebo in the treatment of inflammatory lesions of rosacea for 16 weeks.</li> </ul> <p><b>Secondary Objectives:</b></p> <ul style="list-style-type: none"> <li>To evaluate the efficacy of oral DFD-29 (minocycline HCl 20 mg capsules) in comparison to placebo in the treatment of inflammatory lesions of rosacea for 16 weeks.</li> <li>To evaluate the efficacy of the two dosage strengths of oral DFD-29 (minocycline HCl 20 mg and 40 mg capsules) in comparison to Oraycea<sup>®</sup> (doxycycline 40 mg capsules) in the treatment of inflammatory lesions of rosacea for 16 weeks.</li> <li>To evaluate the safety and tolerability of oral DFD-29 (minocycline HCl 20 mg capsules) in comparison to placebo in the treatment of inflammatory lesions of rosacea for 16 weeks.</li> <li>To evaluate the safety and tolerability of the two dosage strengths of oral DFD-29 (minocycline HCl 20 mg and 40 mg capsules) in comparison to Oraycea<sup>®</sup> (doxycycline 40 mg capsules) in the treatment of inflammatory lesions of rosacea for 16 weeks.</li> <li>To evaluate the efficacy of oral DFD-29 (minocycline HCl 40 mg capsules) in comparison to oral DFD-29 (minocycline HCl 20 mg capsules) in the treatment of inflammatory lesions of rosacea for 16 weeks.</li> </ul>

	<ul style="list-style-type: none"> <li>To evaluate the safety and tolerability of oral DFD-29 (minocycline HCl 40 mg capsules) in comparison to DFD-29 (minocycline HCl 20 mg capsules) in the treatment of inflammatory lesions of rosacea for 16 weeks.</li> </ul>
DESIGN	This is a 16-week, multicenter, controlled, randomized, parallel group, double-blind study. Subjects, who are at least 18 years old, diagnosed with papulopustular rosacea will be randomized to 4 different treatment groups.
TREATMENTS	<p>Each subject will be allocated to one of the following treatment groups, receiving 1 capsule once daily in the morning for 16 weeks:</p> <ol style="list-style-type: none"> <li>DFD-29 (minocycline HCl) Extended Release Capsules (40 mg)</li> <li>DFD-29 (minocycline HCl) Extended Release Capsules (20 mg)</li> <li>Oracea<sup>®</sup> (doxycycline) Modified Release Hard Capsules (40 mg)</li> <li>Placebo Capsules</li> </ol>
SUMMARY OF STUDY DESIGN	<p>After assessing eligibility during an up to 28 days screening period, 200 subjects will be enrolled in the study (fifty subjects each in groups 1 to 4). Subject visits are scheduled at Screening, Baseline (Day 1), and Weeks 4, 8, 12 and 16.</p> <p>Clinical assessments of efficacy will be conducted based on Investigator's Global Assessment (IGA, modified scale without erythema), Clinician's Erythema Assessment (CEA), and on inflammatory lesion counts at Weeks 4, 8, 12 and 16 in comparison to Baseline. Additionally, high sensitivity C-reactive protein (hs-CRP) in the blood will be assessed at Baseline, and at Week 16 to explore any impact of the treatment on the inflammatory pathology.</p> <p>Laboratory assessments on blood (hematology and biochemistry) and urine (routine tests) will be conducted at Screening, Week 4 and Week 16 (End of the study) to assess for any changes in the safety parameters. Other safety assessments include vital signs, physical examination, urine pregnancy tests (only for females with child bearing potential), and collection of adverse event data.</p> <p>Impact of the treatment on the Quality of Life (QoL) of the subjects will be done using the rosacea specific tool RosaQoL at Baseline, and at Weeks 4, 8, 12 and 16.</p>
STUDY POPULATION	Two hundred (200) male and female subjects with papulopustular rosacea will be enrolled to get 176 completed subjects (forty-four (44) completers each in groups 1 to 4).
INCLUSION CRITERIA	<p>The criteria for inclusion are:</p> <ol style="list-style-type: none"> <li>Subjects must be able to understand the requirements of the study and be willing to give written informed consent.</li> <li>Male and female subjects aged 18 years and above.</li> <li>Subjects, any gender or ethnicity (and of Fitzpatrick skin type I – III), must be in good general health as determined by the</li> </ol>

	<p>Investigator.</p> <ol style="list-style-type: none"><li>4. Subjects must have a clinical diagnosis of papulopustular rosacea, IGA grade 2 - 4.</li><li>5. Subjects must have 10 - 40 (both inclusive) inflammatory lesions (papules and pustules) of rosacea over the face.</li><li>6. Subjects must have not more than 2 nodules.</li><li>7. Subjects with moderate to severe erythema with a total score of 5 - 20 on the CEA scale.</li><li>8. Subjects must agree to only use the study products and to not use any other treatment for rosacea (prescription or Over The Counter (OTC)) during the course of the study.</li><li>9. Subjects must be free of any systemic or dermatologic disorder, which in the opinion of the Investigator, will interfere with the study results, and especially free of any skin diseases (for example peri-oral dermatitis, facial keratosis pilaris, seborrheic dermatitis, and acne vulgaris) that may confound the evaluation of rosacea.</li><li>10. Females must have a negative urine pregnancy test at the Screening and Baseline Visit. Sensitivity of such a test should at least be 25 mIU/mL or lower for hCG.</li><li>11. Females must either be postmenopausal with no menses for at least 12 months or surgically sterile (hysterectomy or tubal ligation) or agree to use a highly effective method of contraception with a pearl index of &lt;1% up to 1 month after last dose. Contraception methods with low user dependency should preferably be used, in particular when contraception is introduced as a result of participation in this clinical study. ‘Highly effective’ methods of birth control include:<ul style="list-style-type: none"><li>• combined (estrogen and progesterone containing) hormonal contraception associated with inhibition of ovulation*:<ul style="list-style-type: none"><li>○ oral</li><li>○ intravaginal</li><li>○ transdermal</li></ul></li><li>• progesterone-only hormonal contraception associated with inhibition of ovulation*:<ul style="list-style-type: none"><li>○ oral</li><li>○ injectable</li><li>○ implantable†</li></ul></li><li>• intra-uterine device (IUD) †</li><li>• intra-uterine hormone releasing system (IUS) †</li><li>• bilateral tubular occlusion†</li><li>• vasectomy of sexual partner that was performed at least 90 days prior to Baseline, and has been medically assessed as successful†</li><li>• sexual abstinence<ul style="list-style-type: none"><li>○ Note: Sexually inactive female subjects may be enrolled at the investigator’s discretion provided that they are counseled to refrain from heterosexual intercourse for the</li></ul></li></ul></li></ol>
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	<p>duration of the study and for one month after the last dose, and understand the possible risks involved in getting pregnant during the study.</p> <ul style="list-style-type: none"> <li>* Hormonal methods: If on hormonal contraceptives, must have been on the same hormonal contraceptive product for 3 months (90 days) prior to Baseline and continued on same method and dose throughout the duration of the study. If subject had used hormonal birth control and had stopped, this should have occurred more than 6 months prior to Baseline. Female subjects on low dose oral contraceptives (containing <math>\leq 35</math> <math>\mu\text{g}</math> of ethinyl estradiol or equivalent dose of other estrogens) must use a second form of contraceptive during the study.</li> <li>† Contraception methods that are considered to have low user dependency.</li> </ul> <p>12. Subjects must be in good general health as determined by the investigator and supported by the medical history and normal or not clinically significant abnormal vital signs (blood pressure and pulse). Subjects are eligible at screening if:</p> <ul style="list-style-type: none"> <li>a. Systolic BP <math>\leq 140</math> and <math>\geq 90</math></li> <li>b. Diastolic BP <math>\leq 100</math> and <math>\geq 50</math></li> <li>c. Pulse 50 – 100 bpm inclusive</li> </ul>
<p><b>EXCLUSION CRITERIA</b></p>	<p>Criteria for exclusion are:</p> <ol style="list-style-type: none"> <li>1. Females who are pregnant or nursing or planning to become pregnant during the study.</li> <li>2. Male whose female partner is planning to conceive a child.</li> <li>3. Subjects who have been treated for rosacea within the 30 days prior to the Baseline Visit (e.g. metronidazole, azelaic acid, doxycycline or brimonidine).</li> <li>4. Subjects who have been treated with systemic retinoids within 6 months prior to the Baseline visit.</li> <li>5. Subjects who have participated in a trial involving any investigational product in the 90 days prior to the Baseline Visit.</li> <li>6. Subjects with any disease or medical condition that would interfere with the study outcome or place the subject at undue risk.</li> <li>7. Subjects who use or have used systemic steroids within the 30 days prior to the Baseline Visit or any other immunosuppressive medication.</li> <li>8. Subjects who are on anti-coagulants or those who are likely to require anti-coagulants during the study period.</li> <li>9. Subjects who have used methoxyflurane or other nephrotoxic drugs (as judged by the investigator) within the past 30 days.</li> <li>10. Subjects with known hypersensitivity to minocycline or doxycycline or any component of the study products or against other kinds of tetracyclines.</li> </ol>

	<ol style="list-style-type: none"> <li>11. Subjects with clinically significant abnormal laboratory test that, in the opinion of the investigator, would compromise the subject's safety or ability to participate in the trial.</li> <li>12. Subjects who are unable to comply with study requirements.</li> <li>13. History of organ transplant requiring immunosuppression, HIV, or other immune compromised state.</li> <li>14. Subjects who in the opinion of the investigator or physician performing the initial examination, should not participate in the trial, e.g. due to probable noncompliance or inability to understand the trial and give adequately informed consent.</li> <li>15. Subjects with close affiliation with the investigator (e.g. a close relative) or persons working at the respective trial sites or subjects who are an employee of the sponsor.</li> <li>16. Subjects institutionalized because of legal or regulatory order.</li> <li>17. History of drug or alcohol abuse in the last year.</li> </ol>		
<b>CONCOMITANT MEDICATION</b>	<b>Product</b>	<b>Washout period before Baseline</b>	<b>During Study</b>
	<b>Topical treatments on the face</b>		
	Benzoyl Peroxide (BPO)	14 days	Prohibited
	Antibiotics (e.g. Macrolides, Clindamycin)	14 days	Prohibited
	Anti-rosacea drugs (e.g. Metronidazole, azelaic acid, Brimonidine, Ivermectin)	30 days	Prohibited
	Immunomodulators (including topical calcineurin inhibitors)	30 days	Prohibited
	Corticosteroids	30 days	Prohibited
	Retinoids	14 days	Prohibited
	Astringents or abrasives (OTC scrubs, exfoliating cleansers and products containing salicylic acid and alcohol)	7 days	Prohibited
	Anti-microbial soaps and face wash	Not applicable	Prohibited
	<b>Systemic Treatments</b>		
	Oral antibiotics (eg Minocycline, Doxycycline, Metronidazole or Macrolides)	30 days	Prohibited
	Corticosteroids	30 days	Prohibited
	Immunomodulators	30 days	Prohibited
	Oral Ivermectin	30 days	Prohibited
	Non-steroidal anti-inflammatory drugs (except aspirin at subanalgesic doses (i.e. <325 mg once daily) for subjects requiring platelet aggregation inhibition)	7 days	Chronic use of NSAIDs (>14 days) other than aspirin is prohibited
Niacin at doses >500 mg /day	7 days	Prohibited	
Other systemic drugs used for	30 days	Prohibited	

	<table border="1"> <tr> <td>treatment of rosacea</td> <td></td> <td></td> </tr> <tr> <td>Barbiturates</td> <td>30 days</td> <td>Prohibited</td> </tr> <tr> <td>Rifampicin</td> <td>30 days</td> <td>Prohibited</td> </tr> <tr> <td>Carbamazepine</td> <td>30 days</td> <td>Prohibited</td> </tr> <tr> <td>Phenytoin (Diphenylhydantoin)</td> <td>30 days</td> <td>Prohibited</td> </tr> <tr> <td>Primidone</td> <td>30 days</td> <td>Prohibited</td> </tr> <tr> <td>Cyclosporin</td> <td>30 days</td> <td>Prohibited</td> </tr> <tr> <td>Methoxyflurane</td> <td>30 days</td> <td>Prohibited</td> </tr> </table>	treatment of rosacea			Barbiturates	30 days	Prohibited	Rifampicin	30 days	Prohibited	Carbamazepine	30 days	Prohibited	Phenytoin (Diphenylhydantoin)	30 days	Prohibited	Primidone	30 days	Prohibited	Cyclosporin	30 days	Prohibited	Methoxyflurane	30 days	Prohibited
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Carbamazepine	30 days	Prohibited																							
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Primidone	30 days	Prohibited																							
Cyclosporin	30 days	Prohibited																							
Methoxyflurane	30 days	Prohibited																							
SAFETY / TOLERABILITY ENDPOINTS	<p>The following parameters have been defined as parameters regarding safety and tolerability:</p> <ul style="list-style-type: none"> <li>• Change from Baseline to each scheduled time point up to EOS for vital signs.</li> <li>• Change from Screening up to EOS for physical examination.</li> <li>• Change from Screening up to EOS for clinical laboratory tests.</li> <li>• Treatment-emergent AEs up to EOS.</li> <li>• Treatment-emergent AEs leading to premature discontinuation of study drug.</li> <li>• Treatment-emergent SAEs up to EOS.</li> </ul> <p>For pre-existing conditions, any event that worsens during treatment will be considered treatment-emergent.</p>																								
PRIMARY EFFICACY ENDPOINTS	<p><b>Co-Primary endpoints:</b></p> <ul style="list-style-type: none"> <li>• Proportion of subjects with IGA (modified scale without erythema) ‘treatment success’ – Grade 0 or 1 at the end of study with at least 2 grade reduction from Baseline to Week 16.</li> <li>• Total inflammatory lesion count (sum of papules, pustules, and nodules) reduction from Baseline to Week 16.</li> </ul>																								
SECONDARY EFFICACY ENDPOINTS	<ul style="list-style-type: none"> <li>• Proportion of subjects with at least a 2 grade reduction in IGA (modified scale without erythema) score from Baseline to Week 16</li> <li>• Median change in total RosaQoL score from Baseline to Week 16.</li> </ul>																								
EXPLORATORY EFFICACY ENDPOINTS	<ul style="list-style-type: none"> <li>• Proportion of subjects with IGA (modified scale without erythema) ‘treatment success’ from Baseline to Weeks 4, 8 and 12.</li> <li>• Total inflammatory lesion count (sum of papules, pustules, and nodules) reduction from Baseline to Weeks 4, 8 and 12.</li> <li>• Proportion of subjects with at least a 2 grade reduction in IGA (modified scale without erythema) score from Baseline to Week 4,8 and 12.</li> <li>• Median change in total RosaQoL score from Baseline to Weeks 4, 8 and 12.</li> <li>• Mean change in high sensitivity C-reactive protein (hs-CRP) levels from Baseline compared to Week 16.</li> <li>• Change in Telangiectasia score from Baseline compared to</li> </ul>																								

	<p>Week 16.</p> <ul style="list-style-type: none"> <li>• Proportion of subjects meeting CEA ‘treatment success’ criteria (i.e. a two grade improvement in the CEA scale) at Weeks 4, 8, 12 and 16</li> </ul>
<p>STATISTICAL METHODOLOGY</p>	<p><b>Safety and tolerability</b> Safety and tolerability data will be listed individually and summarized using descriptive statistics and frequency tables. Change from Baseline will be analyzed for the following parameters:</p> <ul style="list-style-type: none"> <li>• Change from Baseline to each scheduled time point up to EOS for vital signs compared between DFD-29, Oraycea® and placebo.</li> <li>• Change from Screening up to EOS for physical examination compared between DFD-29, Oraycea® and placebo.</li> <li>• Change from Screening up to EOS for clinical laboratory tests compared between DFD-29, Oraycea® and placebo.</li> <li>• Treatment-emergent AEs up to EOS compared between DFD-29, Oraycea® and placebo.</li> <li>• Treatment-emergent AEs leading to premature discontinuation of study drug compared between DFD-29, Oraycea® and placebo.</li> <li>• Treatment-emergent SAEs up to EOS compared between DFD-29, Oraycea® and placebo.</li> </ul> <p><b>Efficacy</b> For all endpoints, the comparison of oral DFD-29 (40 mg capsule) versus placebo will be the primary objective of the study. All other comparisons viz, between oral DFD-29 (20 mg capsule) and placebo, between oral DFD-29 (40 and 20 mg capsules) and Oraycea® and between oral DFD-29 40 mg capsules and DFD-29 20 mg capsules, will be treated as secondary.</p> <p><b>Co-Primary Endpoints</b></p> <ul style="list-style-type: none"> <li>• The proportion of subjects with IGA (modified scale without erythema) ‘treatment success’ – will be investigated with a Chi-square test. ‘Treatment Success’ is described as having at least 2 grade reduction from Baseline with grade 0 or 1 at Week 16.</li> <li>• The difference between the treatments in terms of the change from Baseline in the total inflammatory lesion count at Week 16 will be tested using MIXED Model, with the investigator as a random factor.</li> </ul> <p><b>Secondary Endpoints:</b></p> <ul style="list-style-type: none"> <li>• The proportion of subjects with at least a 2 grade reduction in IGA (modified scale without erythema) score from Baseline to Week 16, will be investigated with a Chi-square test.</li> </ul>

	<ul style="list-style-type: none"><li>• Median change in total RosaQoL score from Baseline to Week 16 will be analyzed using ANOVA.</li></ul> <p>Exploratory Endpoints:</p> <ul style="list-style-type: none"><li>• Proportion of subjects with at least a two grade improvement of IGA (modified scale without erythema) grade from Baseline to Weeks 4, 8 and 12 will be investigated with a Chi-square test.</li><li>• The difference between treatments in terms of the change from Baseline in the total inflammatory lesion count at Weeks 4, 8 and 12 will be tested using MIXED Model with the investigator as a random factor.</li><li>• The proportion of subjects with at least a 2 grade reduction in IGA (modified scale without erythema) score from Baseline to Week 4, 8 and 12 will be investigated with a Chi-square test.</li><li>• Median change in total RosaQoL score from Baseline to Weeks 4, 8 and 12 will be investigated using ANOVA.</li><li>• The difference between treatments will be tested for the mean change in high sensitivity C-reactive protein (hs-CRP) levels from Baseline to Week 16 using ANOVA</li><li>• Change in Telangiectasia score from Baseline to Week 16 will be investigated using ANOVA.</li><li>• Proportion of subjects meeting CEA ‘treatment success’ criteria (i.e. a two grade improvement in the CEA scale) in the treatment groups at Weeks 4, 8, 12 and 16 will be investigated using ANOVA.</li></ul> <p>Exploratory analyses for the following subgroups will be performed:</p> <ul style="list-style-type: none"><li>• Male versus female.</li><li>• Mild (score 2), moderate (score 3) and severe (score 4) IGA score.</li><li>• Normal hs-CRP versus abnormal hs-CRP at Baseline.</li></ul>
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**Table 1: Visit and Assessment Schedule**

	Visit 1	Visit 2	Phone call	Visit 3	Visit 4	Visit 5	Visit 6
	Screening	Baseline	Week 2	Week 4	Week 8	Week 12	Week 16 Early termination
Study Day	Day -30 to Day -3	Day 1	Day 15 (+/- 2 days)	Day 29 (+/- 5 days)	Day 57 (+/- 5 days)	Day 85 (+/- 5 days)	Day 113 (+/- 5 days)
Informed Consent	X						
Demographic Data including Fitzpatrick Skin Type	X						
Inclusion and Exclusion Criteria	X						
Eligibility Conclusion		X	X	X	X	X	X
Weight	X	X					X
Height	X						
Medical History/ Prior Medications	X	X					
Vital Signs (BP, Pulse rate)	X	X		X	X	X	X
Urine Pregnancy Test (for females of childbearing potential)	X	X		X	X	X	X
IGA	X	X		X	X	X	X
CEA	X	X		X	X	X	X
Lesion count	X	X		X	X	X	X
Telangiectasia	X	X		X	X	X	X
RosaQoL Score	X	X		X	X	X	X
Physical Examination	X						X
Laboratory assessments (Blood & Urine)	X			X			X
hs-CRP		X					X
Randomization		X					
Dispense Study Drug		X		X	X	X	
Dispense/Review/Collect Study Diary		X		X	X	X	X
Discussion of Subject Instructions		X		X	X	X	
Collect Study Drug				X	X	X	X
Evaluate Study Drug Compliance			X	X	X	X	X
Adverse Event (Assessment/Collection)		X	X	X	X	X	X
Concomitant Medication			X	X	X	X	X
End of Study							X
Telephonic enquiry of well-being and medication compliance			X				

## 6 INTRODUCTION AND RATIONALE

### 6.1 Introduction

Rosacea is a chronic relapsing inflammatory cutaneous disorder, primarily of the convexities of the central face (cheeks, chin, nose, and central forehead). The main clinical forms of the disease are erythematotelangiectatic rosacea (ETR; subtype 1), papulopustular rosacea (PPR; subtype 2), phymatous rosacea (PHY; subtype 3), and ocular rosacea (subtype 4) (Wilkin *et al*, 2002). In addition to the classification system, the National Rosacea Society Expert Committee on the Classification and Staging of Rosacea devised a standard method for assessing gradations of the severity of rosacea (Wilkin *et al*, 2004). This standard grading system is essential to perform research, analyze results, and compare data; provides a common reference for diagnosis, treatment, and assessment of results in clinical practice; and is the basis for the Investigator's Global Assessment (IGA) in rosacea.

Rosacea is a common disorder with a prevalence of 12,3% in the general population of Germany according to a recent population-based epidemiological study (Tan *et al*, 2016). The prevalence of rosacea is highest in subjects of northern European or Celtic heritage and shows a South to North increase in Europe, ranging from 2% to more than 10% and 20% in general and working populations, respectively (Abram *et al*, 2010; Tan *et al*, 2016). An overall incidence rate of 1.65 per 1000 person-years was reported for diagnosed rosacea (Spoendlin *et al*, 2012). However, the RISE study showed that over 80% of the cases were not previously diagnosed (Tan *et al*, 2016). Although subjects with fair skin (Fitzpatrick skin phenotypes I–III) are more likely to be affected, it can be diagnosed in subjects with skin of any color. Rosacea occurs in both men and women at any age, but is more common among female subjects and its incidence peaks between the ages of 30 and 50 years.

The pathogenesis of rosacea is poorly understood. Contributing factors may include immune and inflammatory abnormalities, vascular alterations, neurogenic dysregulation, presence of cutaneous microorganisms, ultraviolet (UV) damage, and skin barrier dysfunction (Feldman *et al*, 2014; Holmes and Steinhoff, 2016; Steinhoff *et al*, 2011; Vemuri *et al*, 2015; Wollina, 2014). Clinical features and trigger factors of rosacea indicate a complex dysregulation of inflammatory, vascular, and neuronal systems at an early stage. Elevated levels of antimicrobial peptides (Cathelicidins), processing enzymes (epidermal serine protease kallikrein 5), pro-inflammatory cytokines, C reactive protein, and toll-like receptors (TLR) seem to play a role in maintaining chronic inflammation in rosacea, which may induce modification of dermal structures mediated by vascular changes and collagen degeneration. Complex vascular mechanisms contribute to local vasodilation, angiogenesis and tissue fibrosis in rosacea. The involvement of the nervous system is supported by the fact that symptoms of rosacea are triggered when subjects are under emotional stress.

Consistent with its immuno-inflammatory and neurovascular pathophysiology, rosacea was found to be associated with several autoimmune diseases (Egeberg *et al*, 2016a), with cardiovascular disease risk factors and cardiovascular diseases (Duman *et al*, 2014; Hua *et al*, 2015), with migraine (Spoendlin *et al*, 2013), and with a 2- to 5-fold increased risk of depression and anxiety disorders (Gupta *et al*, 2005; Egeberg *et al*, 2016b). In addition,

almost half of the rosacea subjects report a significant impairment in their quality of life (Bewley *et al*, 2016; Tan *et al*, 2016). Taken into consideration these findings and that about 50% of the subjects receive no rosacea care, effective treatment might contribute not only to symptomatic relief, but also to reduce cardiovascular risk and to improve the emotional health and the quality of life of subjects with rosacea.

Oral tetracyclines, especially doxycycline and minocycline, have been a cornerstone of systemic treatment in rosacea. Independently of their antibacterial properties, tetracyclines at low doses exert anti-inflammatory effects, decrease matrix metalloproteinase activity involved in kallikrein activation, act as oxygen scavengers, and improve epidermal barrier function. All these biological activities could contribute to the effectiveness of low-dose tetracyclines in rosacea treatment. The use of tetracyclines was also found to be associated with a decreased incidence of vascular disease in veterans with rosacea (Dosal *et al*, 2014).

## 6.2 Study Rationale

This is a multi-center, randomized, double-blind, parallel-group, controlled study to assess the efficacy, safety and tolerability of two dosage strengths of oral DFD-29 (minocycline HCl) Extended Release Capsules compared to placebo and Oraycea<sup>®</sup> Modified Release Hard Capsules for the treatment of inflammatory lesions of rosacea for 16 weeks.

Papulopustular rosacea is the second most common form of the disease and represents a more inflammatory subtype, characterized by persistent central facial erythema with transient papules or pustules or both in a central facial distribution, but it can also present with telangiectases (usually masked by its typical manifestations) and occur concomitantly with acne vulgaris (Wilkin *et al*, 2002; Wollina, 2014). In northern European countries, the papulopustular subtype represents one fourth to one third of the rosacea cases (Abram *et al*, 2010; Tan *et al*, 2016). Although there are multiple therapeutic options available for the treatment of papulopustular rosacea, the most widely used systemic agents are oral tetracycline derivatives, particularly doxycycline and minocycline.

The main concern with the long-term use of tetracyclines in rosacea has been antibacterial resistance. However, the recent findings that tetracyclines exert anti-inflammatory effects and seem to be effective in papulopustular rosacea at low sub-antimicrobial doses opens new options for its clinical use in this indication that warrant further investigation (Feldman *et al*, 2014; Garrido-Mesa *et al*, 2013; Griffin *et al*, 2010; van Zuuren *et al*, 2015). Doxycycline and minocycline show a variety of biological actions independent of their antibiotic activity, including scavenging of oxygen radicals, anti-inflammatory and anti-apoptotic actions, and inhibition of proteolysis, angiogenesis and tumor growth. Tetracyclines may reduce the inflammation associated with rosacea by downregulating proinflammatory cytokines and inhibiting matrix metalloproteinases involved in kallikrein activation (Feldman *et al*, 2014; Garrido-Mesa *et al*, 2013; Griffin *et al*, 2010).

Minocycline modulates glutamate-induced excitotoxicity and has anti-apoptotic, antioxidant, anti-inflammatory and neuroprotective effects that proved beneficial in experimental models of various diseases with an inflammatory basis, including dermatological, autoimmune, vascular, psychiatric and neurological conditions, for which it has been postulated as an

adjunctive therapy (Garrido-Mesa *et al*, 2013; Griffin *et al*, 2010; Dean *et al*, 2014). The lack of photosensitivity represents a potential advantage of minocycline for the treatment of papulopustular rosacea because doxycycline exhibits a dose-related phototoxicity (Del Rosso, 2015). Minocycline demonstrated benefit in the treatment of inflammatory lesions in subjects with rosacea (Jackson *et al*, 2014; van Zuuren *et al*, 2015) and proved remarkably effective in decreasing serum C-reactive protein (CRP) levels in other conditions (Kanai *et al*, 2009). However, the dose-related efficacy of minocycline at sub-antimicrobial doses in improving the clinical symptoms and reducing serum CRP in papulopustular rosacea has not been investigated.

### 6.2.1 Dose Selection

The proposed dose strengths of DFD-29 to be evaluated in this study are 20 mg and 40 mg. Currently there is no data available on the safety and efficacy of any of DFD-29 dose strengths, when used in patients of rosacea. Minocycline, along with doxycycline and tetracycline, has found a place in dermatologists' therapeutic armamentarium, for treatment of inflammatory lesions (papules and pustules) in patients with moderate to severe rosacea; however, only sub-antimicrobial dose doxycycline has been approved in the US and EU for the above-mentioned indication.

The rationale of selecting DFD-29 doses lower than the approved minocycline dose on mg/kg body weight basis, is based on the lower protein binding and higher lipophilicity of minocycline, as compared to doxycycline, which is expected to lead to higher tissue penetration and exposures of minocycline than those achieved for doxycycline with the 40 mg oral dose used for rosacea. Assuming comparable anti-inflammatory effects, similar or higher exposure of minocycline achieved using the proposed DFD-29 doses are postulated to translate into efficacy at least similar to doxycycline 40 mg that is approved for rosacea.

### 6.2.2 Ethical Conduct of the Study

The study will be performed in accordance with the protocol, ICH Harmonized Tripartite Guidelines for Good Clinical Practice (GCP), the principles of the "Declaration of Helsinki" (as amended in Tokyo, Venice, Hong Kong, Somerset-West, Edinburgh, Washington DC, Tokyo, Seoul and Fortaleza), and applicable local regulations. Please refer to Section 11.2 (Good Clinical Practice) for further ethical considerations.

## 7 STUDY OBJECTIVES

### Primary Objectives:

- To evaluate the efficacy of oral DFD-29 (minocycline HCl 40 mg capsules) in comparison to placebo in the treatment of inflammatory lesions of rosacea for 16 weeks.
- To evaluate the safety and tolerability of oral DFD-29 (minocycline HCl 40 mg capsules) in comparison to placebo in the treatment of inflammatory lesions of rosacea for 16 weeks.

### Secondary Objectives:

- To evaluate the efficacy of oral DFD-29 (minocycline HCl 20 mg capsules) in comparison to placebo in the treatment of inflammatory lesions of rosacea for 16 weeks.
- To evaluate the efficacy of the two dosage strengths of oral DFD-29 (minocycline HCl 20 mg and 40 mg capsules) in comparison to Oraycea<sup>®</sup> (doxycycline 40 mg capsules) in the treatment of inflammatory lesions of rosacea for 16 weeks.
- To evaluate the safety and tolerability of oral DFD-29 (minocycline HCl 20 mg capsules) in comparison to placebo in the treatment of inflammatory lesions of rosacea for 16 weeks.
- To evaluate the safety and tolerability of the two dosage strengths of oral DFD-29 (minocycline HCl 20 mg and 40 mg capsules) in comparison to Oraycea<sup>®</sup> (doxycycline 40 mg capsules) in the treatment of inflammatory lesions of rosacea for 16 weeks.
- To evaluate the efficacy of oral DFD-29 (minocycline HCl 40 mg capsules) in comparison to oral DFD-29 (minocycline HCl 20 mg capsules) in the treatment of inflammatory lesions of rosacea for 16 weeks.
- To evaluate the safety and tolerability of oral DFD-29 (minocycline HCl 40 mg capsules) in comparison to DFD-29 (minocycline HCl 20 mg capsules) in the treatment of inflammatory lesions of rosacea for 16 weeks.

## 8 STUDY DESIGN

### 8.1 Overall Study Design

This is a 16-week, multicenter, controlled, randomized, parallel group, double-blind study. Subjects, who are at least 18 years old and diagnosed with papulopustular rosacea will be randomized to one of the following treatments:

1. DFD-29 (minocycline HCl) Extended Release Capsules (40 mg) once daily for 16 weeks
2. DFD-29 (minocycline HCl) Extended Release Capsules (20 mg) once daily for 16 weeks
3. Oraycea<sup>®</sup> (doxycycline) Modified Release Hard Capsules (40 mg) once daily for 16 weeks
4. Placebo capsules once daily for 16 weeks

After assessing eligibility during an up to 28-days screening period, 200 subjects will be enrolled in the study (fifty (50) subjects each in groups 1 to 4) in order to get 176 completed subjects (forty four (44) completers each in group).

The investigational products will be taken orally. Subject visits are scheduled at Screening, Baseline (Day 1), and Weeks 4, 8, 12 and 16. Clinical assessments of efficacy will be conducted based on Investigator's Global Assessment (IGA, modified scale without erythema), Clinician's Erythema Assessment (CEA), RosaQoL Score and on inflammatory lesion counts at Weeks 4, 8, 12 and 16 in comparison to Baseline. Additionally, high sensitivity C-reactive protein (hs-CRP) in the blood will be assessed at Baseline, and at Week 16 to explore any impact of the treatment on the inflammatory pathology.

Laboratory assessments on blood (hematology and biochemistry) and urine (routine tests) will be conducted at Screening, Week 4 and Week 16 (End of the study) to assess for any changes in the safety parameters. Other safety assessments include vital signs, physical examination, urine pregnancy tests (only for females with child bearing potential), and collection of adverse event data. Impact of the treatment on the Quality of Life (QoL) of the subjects will be done using a rosacea specific tool RosaQoL at Baseline, and at Weeks 4, 8, 12 and 16.

#### 8.1.1 Informed Consent

After adequate explanation of the aims, methods, objectives of the study and potential hazards of the study drug, a written informed consent from each individual participating in this study will be obtained. Informed consent must be obtained before a subject can participate in the study, prior to performing any study related procedures and before withdrawal of any therapies prohibited during the study. The consent form must be signed and dated by the subject and by the Investigator who obtained the subject's informed consent. A copy of the signed and dated consent form must be given to the subject and the date of the consent process and the name of the study personnel who conducted the consent process must be documented in the source document. Please refer to Section [11.2.3](#) for further ethical considerations.

The Investigator may need to inform a potential subject well in advance of the actual date of Screening that he/she needs to avoid certain drugs/therapies to comply with the Washout.

## 8.1.2 Baseline Parameters and Concomitant Medications

### 8.1.2.1 Screening (Visit 1)

The following Baseline and subject characteristics are collected as part of the Screening:

- Informed Consent for participation in the study
- Medical History (all relevant medical history including medication will be documented, including the previous therapy for the study indication)
- Baseline demographics including sex, date of birth, ethnicity, weight, height, and Fitzpatrick Skin Type
- Laboratory assessments on blood (hematology, serology and clinical chemistry) and urine (routine tests) (Section 8.1.3.7)
- Evaluation of vital sign parameters (Section 8.1.3.4)
- Physical examination (Section 8.1.3.5)
- Urine pregnancy test (Section 8.1.5)
- IGA (Section 8.1.4.1)
- CEA (Section 8.1.4.3)
- RosaQoL (Section 8.1.4.4)
- Total inflammatory lesion count Section (8.1.4.2)
- Telangiectasia score evaluation (Section 8.1.4.6)
- Inclusion and Exclusion Criteria (Sections 8.2.1 and 8.2.2)

### 8.1.2.2 Baseline (Visit 2)

The following assessments are being conducted at Baseline:

- Eligibility conclusion (based on inclusion (Section 8.2.1) and exclusion criteria (Section 8.2.2))
- Confirmation of Medical History (all relevant medical history including medication will be documented)
- Weight
- Review of AEs (Section 8.1.3.2)
- Blood sampling for hs-CRP assessment (Section 8.1.4.5)
- Urine pregnancy test (Section 8.1.5)
- Evaluation of vital sign parameters (Section 8.1.3.4)
- IGA (Section 8.1.4.1)
- CEA (Section 8.1.4.3)
- RosaQoL (Section 8.1.4.4)
- Total inflammatory lesion count (Section 8.1.4.2)
- Telangiectasia score evaluation (Section 8.1.4.6)
- Randomization
- Dispensing of study drug
- Dispensing of study diary
- Discussion of subject instructions

### 8.1.2.3 Prior and Concomitant Medications

All medications taken within 3 months before Screening should be recorded on the Prior Medications page.

All medications that are stopped to provide the required washout should be recorded on the Prior Medications page.

All medications previously used for the study indication will be recorded on the Prior Medications page.

All medications taken during the study or started during the course of the study should be recorded on the Concomitant Medications Page.

Concomitant medications initiated, stopped, up-titrated or down-titrated for an AE (Adverse Event) will be recorded on a specific Concomitant Medications page.

### **8.1.3 Safety and Tolerability Assessments**

Laboratory assessments on blood (hematology and biochemistry) and urine (routine tests) will be conducted at Screening, Week 4 and Week 16 (End of the study). A physical examination will be conducted at Screening and Week 16 (End of the study) to assess for any changes in the safety parameters. Other safety assessments include vital signs (blood pressure, pulse rate), urine pregnancy tests for women of child bearing potential and collection of adverse event data which will be conducted at every visit. A study diary will be dispensed and collected at every visit starting at the Baseline Visit. AE data, concomitant medication, and compliance data from the diary will be entered in the eCRF.

The definitions, reporting, and Follow-up of AEs and SAEs are described in Section 9.

[Table 1](#) provides an overview of all time points on which safety assessments will be performed.

A detailed description of the scheduled tasks at each visit can be found in [Table 1](#) and Sections [8.1.2](#) and [8.1.3](#). Enough time should be reserved for all assessments to be performed.

#### **8.1.3.1 Activities scheduled at Individual Study Visits**

##### **Week 2 (Phone call)**

- Eligibility confirmation (based on inclusion ([Section 8.2.1](#)) and exclusion criteria ([Section 8.2.2](#)))
- Review of AEs ([Section 8.1.3.2](#))
- Use of Concomitant Medication ([Section 8.2.3.1](#))
- Evaluation of study drug compliance
- Telephonic enquiry of well-being and medication compliance

##### **Week 4 (Visit 3)**

- Eligibility confirmation (based on inclusion ([Section 8.2.1](#)) and exclusion criteria ([Section 8.2.2](#)))
- Review of AEs ([Section 8.1.3.2](#))
- Use of Concomitant Medication ([Section 8.2.3.1](#))
- Urine pregnancy test ([Section 8.1.5](#))
- Evaluation of vital sign parameters ([Section 8.1.3.4](#))
- IGA ([Section 8.1.4.1](#))
- CEA ([Section 8.1.4.3](#))
- RosaQoL ([Section 8.1.4.4](#))
- Total inflammatory lesion count ([Section 8.1.4.2](#))

- Telangiectasia score evaluation (Section 8.1.4.6)
- Laboratory assessments on blood (hematology and clinical chemistry) and urine (routine tests) (Section 8.1.3.7)
- Collection of study drug
- Evaluate study drug compliance
- Dispensing of study drug
- Collection, review and dispensing of study diary
- Discussion of subject instructions

#### Week 8 (Visit 4)

- Eligibility confirmation (based on inclusion (Section 8.2.1) and exclusion criteria (Section 8.2.2))
- Review of AEs (Section 8.1.3.2)
- Use of Concomitant Medication (Section 8.2.3.1)
- Urine pregnancy test (Section 8.1.5)
- Evaluation of vital sign parameters (Section 8.1.3.4)
- IGA (Section 8.1.4.1)
- CEA (Section 8.1.4.3)
- RosaQoL (Section 8.1.4.4)
- Total inflammatory lesion count (Section 8.1.4.2)
- Telangiectasia score evaluation (Section 8.1.4.6)
- Collection of study drug
- Evaluate study drug compliance
- Dispensing of study drug
- Collection, review and dispensing of study diary
- Discussion of subject instructions

#### Week 12 (Visit 5)

- Eligibility confirmation (based on inclusion (Section 8.2.1) and exclusion criteria (Section 8.2.2))
- Review of AEs (Section 8.1.3.2)
- Use of Concomitant Medication (Section 8.2.3.1)
- Urine pregnancy test (Section 8.1.5)
- Evaluation of vital sign parameters (Section 8.1.3.4)
- IGA (Section 8.1.4.1)
- CEA (Section 8.1.4.3)
- RosaQoL (Section 8.1.4.4)
- Total inflammatory lesion count (Section 8.1.4.2)
- Telangiectasia score evaluation (Section 8.1.4.6)
- Collection of study drug
- Evaluate study drug compliance
- Dispensing of study drug
- Collection, review and dispensing of study diary
- Discussion of subject instructions

#### Week 16/End of Study or early termination (Visit 6)

- Eligibility confirmation (based on inclusion (Section 8.2.1) and exclusion criteria (Section 8.2.2))
- Review of AEs (Section 8.1.3.2)
- Use of Concomitant Medication (Section 8.2.3.1)
- Weight (Section 8.1.3.6)
- Physical examination (Section 8.1.3.5)
- Blood sampling for hs-CRP assessment (Section 8.1.4.5)
- Laboratory assessments on blood (hematology and clinical chemistry) and urine (routine tests) (Section 8.1.3.7)
- Urine pregnancy test (Section 8.1.5)
- Evaluation of vital sign parameters (Section 8.1.3.4)
- IGA (Section 8.1.4.1)
- CEA (Section 8.1.4.3)
- RosaQoL (Section 8.1.4.4)
- Total inflammatory lesion count (Section 8.1.4.2)
- Telangiectasia score evaluation (Section 8.1.4.6)
- Collection of study drug
- Evaluate study drug compliance
- Collection, and review of study diary

#### 8.1.3.2 Adverse Events

Adverse events will be recorded according to GCP requirements. For the safety analysis, only treatment-emergent adverse events will be analyzed. Treatment-emergent adverse events will include any AE occurring during the treatment period (from the first administration of the study drug until the end of study). For pre-existing conditions, any event that worsens during treatment will be considered treatment-emergent.

#### 8.1.3.3 Telephonic Enquiry

At Week 2, a telephonic enquiry will be scheduled to assess the well-being of the subjects and study drug compliance.

#### 8.1.3.4 Vital Signs

Blood pressure (systolic and diastolic) will be measured in sitting position, at least 5 minutes after assuming a sitting position and having rested. Pulse rate will be measured at the time of vital sign assessment.

#### 8.1.3.5 Physical Examination

The physical examination will include general appearance, skin, eyes, ear/nose/throat, head and neck, heart, chest and lungs, abdomen, extremities, lymph nodes, musculoskeletal, neurological, and other body systems, if applicable, for describing the status of the subject's health.

#### 8.1.3.6 Weight and Height

The subject's body weight will be measured using an accurate balance. The balance should have a precision of at least 0.5 kg. Body weight will be recorded with 1 decimal. The subject's height and weight is measured without wearing shoes.

### 8.1.3.7 Laboratory Assessments

Clinically significant laboratory abnormalities after screening must be reported by the investigator as an AE or SAE, as appropriate (see Section 9).

As a rule, the blood samples will be taken from the subject by puncture of a vein in the cubital or the antebrachial region. The samples will be sent to the central laboratory for analysis. Details regarding overall blood volume collected, sample handling and shipment will be provided in a separate Laboratory manual. A summary of the routine tests conducted in this study (see Table 1) can be found in Table 2, any other investigation (including anti-nuclear antibody and hepatic transaminases for suspected drug-induced lupus or auto-immune hepatitis in symptomatic subjects) will have to be symptom-driven or on Investigator judgment on a case to case basis.

Additional safety samples may be taken at investigator discretion in consultation with the sponsor.

**Table 2: Summary of Clinical Laboratory Tests**

Hematology	Chemistry	Urinalysis	Others
Complete Blood Count (CBC)	Glucose Uric acid Calcium Sodium Potassium Chloride Alkaline phosphatase Total bilirubin Creatinine BUN AST (SGOT) ALT(SGPT) LDH Total protein Albumin	Urobilinogen <sup>a</sup> Nitrites <sup>a</sup> pH <sup>a</sup> Glucose <sup>a</sup> Protein <sup>a</sup> Blood <sup>a</sup> Ketones <sup>a</sup> Pregnancy <sup>b</sup>	hs-CRP Serology (for anti-HIV I, anti-HIV 2, HBsAG, and anti-HCV antibodies)

<sup>a</sup> Dip stick.

<sup>b</sup> Only required for women of child bearing potential

### 8.1.4 Efficacy Assessments

#### 8.1.4.1 Investigator’s Global Assessment (IGA)

The IGA (see Appendix 13.1) is carried out by visual inspection by the Investigator at every study visit from Screening up to Week 16 (or at early termination).

#### 8.1.4.2 Total Inflammatory Lesion Count

The total inflammatory lesion count is carried out by visual inspection by the Investigator at every study visit from Screening up to Week 16 (or at early termination). Inflammatory lesions will be recorded on a diagram of a human face, divided in 4 quadrants.

#### 8.1.4.3 Clinician’s Erythema Assessment (CEA)

The CEA is carried out by visual inspection by the Investigator at every study visit from Screening up to Week 16 (or at early termination). The erythema assessment will be carried out separately at 5 locations on the face- forehead, nose, chin, right cheek and left cheek. The scores from all 5 locations will be totaled to yield the final CEA grade.

#### 8.1.4.4 Rosacea Quality of Life (RosaQoL)

The RosaQoL assessment is carried out by the Investigator by asking questions as per the validated RosaQoL questionnaire instrument, at every study visit from Screening up to Week 16 (or at early termination). The subjects will have to rate on a 5 grade scale their perception of the impact that Rosacea has on various dimensions influencing their quality of life.

#### 8.1.4.5 High sensitive C-reactive Protein (hs-CRP)

Blood will be drawn for the analysis of hs-CRP at Baseline and Week 16.

#### 8.1.4.6 Telangiectasia Score

Telangiectasia will be graded by visual inspection by the Investigator at every study visit from Screening up to Week 16 (or at early termination).

### 8.1.5 Pregnancy test

A urine pregnancy test will be performed for women of child bearing potential at every study visit from Screening up to Week 16 (or at early termination if previous pregnancy testing was performed more than 28 days prior).

## 8.2 Study Population

The subject population will include human subjects, who are at least 18 years old, diagnosed with papulopustular rosacea and satisfy all entry criteria.

### 8.2.1 Inclusion Criteria

The following criteria must be met by all subjects considered for study participation:

1. Subjects must be able to understand the requirements of the study and be willing to give written informed consent.
2. Male and female subjects aged 18 years and above.
3. Subjects, any gender or ethnicity (and of Fitzpatrick skin type I – III), must be in good general health as determined by the Investigator
4. Subjects must have a clinical diagnosis of papulopustular rosacea, IGA grade 2 - 4.
5. Subjects must have 10 - 40 (both inclusive) inflammatory lesions (papules and pustules) of rosacea over the face.
6. Subjects must have not more than 2 nodules.
7. Subjects with moderate to severe erythema with a total score of 5 - 20 on the CEA scale.
8. Subjects must agree to only use the study products and to not use any other treatment for rosacea (prescription or Over The Counter (OTC)) during the course of the study.
9. Subjects must be free of any systemic or dermatologic disorder, which in the opinion of the Investigator, will interfere with the study results, and especially free of any skin diseases (for example peri-oral dermatitis, facial keratosis pilaris, seborrheic dermatitis, and acne vulgaris) that may confound the evaluation of rosacea.
10. Females must have a negative urine pregnancy test at the Screening and Baseline Visit. Sensitivity of such a test should at least be 25 mIU/mL or lower for hCG.
11. Females must either be postmenopausal with no menses for at least 12 months or surgically sterile (hysterectomy or tubal ligation) or agree to use a highly effective method of contraception with a pearl index of <1% up to 1 month after last dose<sup>1</sup>.

Contraception methods with low user dependency should preferably be used, in particular when contraception is introduced as a result of participation in this clinical study.

‘Highly effective’ methods of birth control include:

- combined (estrogen and progesterone containing) hormonal contraception associated with inhibition of ovulation\*:
  - oral
  - intravaginal
  - transdermal
- progesterone-only hormonal contraception associated with inhibition of ovulation\*:
  - oral
  - injectable
  - implantable†
- intra-uterine device (IUD) †
- intra-uterine hormone releasing system (IUS) †
- bilateral tubular occlusion†
- vasectomy of sexual partner that was performed at least 90 days prior to Baseline, and has been medically assessed as successful†
- sexual abstinence
  - Note: Sexually inactive female subjects may be enrolled at the investigator’s discretion provided that they are counseled to refrain from heterosexual intercourse for the duration of the study and for one month after the last dose, and understand the possible risks involved in getting pregnant during the study.

\* Hormonal methods: If on hormonal contraceptives, must have been on the same hormonal contraceptive product for 3 months (90 days) prior to Baseline and continued on same method and dose throughout the duration of the study. If subject had used hormonal birth control and had stopped, this should have occurred more than 6 months prior to Baseline. Female subjects on low dose oral contraceptives (containing  $\leq 35$   $\mu\text{g}$  of ethinyl estradiol or equivalent dose of other estrogens) must use a second form of contraceptive during the study.

† Contraception methods that are considered to have low user dependency.

12. Subjects must be in good general health as determined by the investigator and supported by the medical history and normal or not clinically significant abnormal vital signs (blood pressure and pulse). Subjects are eligible at screening if:
- a. Systolic BP  $\leq 140$  and  $\geq 90$
  - b. Diastolic BP  $\leq 100$  and  $\geq 50$
  - c. Pulse 50 – 100 bpm inclusive

### 8.2.2 Exclusion Criteria

Subjects will be excluded if they meet any of the following criteria:

1. Females who are pregnant or nursing or planning to become pregnant during the study.
2. Male whose female partner is planning to conceive a child.
3. Subjects who have been treated for rosacea within the 30 days prior to the Baseline Visit (e.g. metronidazole, azelaic acid, doxycycline or brimonidine).
4. Subjects who have been treated with systemic retinoids within 6 months prior to the Baseline visit.

5. Subjects who have participated in a trial involving any investigational product in the 90 days prior to the Baseline Visit.
6. Subjects with any disease or medical condition that would interfere with the study outcome or place the subject at undue risk.
7. Subjects who use or have used systemic steroids within the 30 days prior to the Baseline Visit or any other immunosuppressive medication.
8. Subjects who are on anti-coagulants or those who are likely to require anti-coagulants during the study period.
9. Subjects who have used methoxyflurane or other nephrotoxic drugs (as judged by the investigator) within the past 30 days.
10. Subjects with known hypersensitivity to minocycline or doxycycline or any component of the study products or against other kinds of tetracyclines.
11. Subjects with clinically significant abnormal laboratory test that, in the opinion of the investigator, would compromise the subject's safety or ability to participate in the trial.
12. Subjects who are unable to comply with study requirements.
13. History of organ transplant requiring immunosuppression, HIV, or other immune compromised state.
14. Subjects who in the opinion of the investigator or physician performing the initial examination, should not participate in the trial, e.g. due to probable noncompliance or inability to understand the trial and give adequately informed consent.
15. Subjects with close affiliation with the investigator (e.g. a close relative) or persons working at the respective trial sites or subjects who are an employee of the sponsor.
16. Subjects institutionalized because of legal or regulatory order.
17. History of drug or alcohol abuse in the last year.

### 8.2.3 Diet, Activities, and Other Restrictions

#### 8.2.3.1 Concomitant Medication

Drugs that influence the inflammatory lesions in acne and rosacea must be avoided. Facial procedures, influencing acne and rosacea [such as chemical peel, photodynamic therapy, acne surgery, cryodestruction or chemodestruction, x-ray therapy, intralesional steroids, dermabrasion, or depilation (except eyebrow shaping), laser therapy or Intense Pulse Light Treatment as well as other procedures on face (Thermage<sup>®</sup> etc.)] are prohibited from 45 days prior to the intake of study medication throughout the whole study period.

Systemic retinoids (including high dose vitamin A >10,000 units per day) must be avoided from 180 days prior to the intake of study medication throughout the whole study period. Furthermore, drugs interacting with minocycline and Oracea<sup>®</sup> or affecting their absorption should also be avoided. Some non-drug therapies should be avoided as well. For details on prohibited topical drugs, systemic drugs and other therapies, see [Table 3](#).

**Table 3: Prohibited Topical Drugs, Systemic Drugs, and Other Treatments**

Product	Washout period before Baseline	During Study
<b>Topical treatments on the face</b>		
Benzoyl Peroxide (BPO)	14 days	Prohibited
Antibiotics (eg. Macrolides, Clindamycin, etc. )	14 days	Prohibited
Anti-rosacea drugs (eg Metronidazole, azelaic acid, Brimonidine, Ivermectin)	30 days	Prohibited
Immunomodulators (including topical calcineurin inhibitors)	30 days	Prohibited
Corticosteroids	30 days	Prohibited
Retinoids	14 days	Prohibited
Astringents or abrasives (OTC scrubs, exfoliating cleansers and products containing salicylic acid and alcohol)	7 days	Prohibited
Anti-microbial soaps and face wash	Not applicable	Prohibited
<b>Systemic Treatments</b>		
Oral antibiotics ( eg Minocycline, Doxycycline, Metronidazole or Macrolides)	30 days	Prohibited
Corticosteroids	30 days	Prohibited
Immunomodulators	30 days	Prohibited
Oral Ivermectin	30 days	Prohibited
Non-steroidal anti-inflammatory drugs (except aspirin at subanalgesic doses (i.e. <325 mg once daily) for subjects requiring platelet aggregation inhibition)	7 days	Chronic use of NSAIDs (>14 days) other than aspirin is prohibited
Niacin at doses >500 mg /day	7 days	Prohibited
Other systemic drugs used for treatment of rosacea	30 days	Prohibited
Barbiturates	30 days	Prohibited
Rifampicin	30 days	Prohibited
Carbamazepine	30 days	Prohibited
Phenytoin (Diphenylhydantoin)	30 days	Prohibited
Primidone	30 days	Prohibited
Cyclosporin	30 days	Prohibited
Methoxyflurane	30 days	Prohibited

#### 8.2.3.2 Dietary Aspects

Substances which can potentially interfere with absorption of minocycline like antacids, multivitamins or other products containing aluminum, magnesium and calcium, oral iron preparations, bismuth subsalicylate and milk and other dairy products should be avoided from 1.5 hours before to 3.0 hours after intake of DFD-29.

#### 8.2.3.3 Sun Exposure

Excessive sun exposure and/or UV radiation should be avoided and protective measures should be taken.

#### 8.2.3.4 Contraceptives

Special attention has to be paid to female subjects taking low dose oral contraceptives (35 microgram of ethinyl estradiol or equivalent dose of other estrogens) as their effectiveness may be affected by the use of DFD-29. To avoid contraceptive failure, females have to use a second acceptable form of contraceptive from Screening up to 1 month after last dose.

Note: ‘Acceptable’ method of contraception include double barrier methods (e.g. a combination of male condom with either cap, diaphragm or sponge with spermicide) in addition to the ‘highly effective methods of birth control that are described in Section 8.2.1, inclusion criterion 11.

Male subjects are requested to be either sexually inactive, sterile or use a barrier method for contraception. Sperm and blood donation is prohibited from Baseline up to 1 month after last study drug intake. Female partners of male subjects have to adopt a highly effective method of contraception with a failure rate of <1 percent per year when used consistently and correctly.

Please refer to inclusion criterion 11 (Section 8.2.1) for further details on contraception for females.

### 8.3 Study Drugs

Study drugs include the investigational products DFD-29 (minocycline HCl) Extended Release Capsules (20 mg and 40 mg), matching placebo and Oraycea<sup>®</sup> (doxycycline) Modified Release Hard Capsules administered during the study.

#### 8.3.1 Investigational Product and Matching Comparators

Dr. Reddy’s will provide DFD-29 (minocycline HCl) Extended Release Capsules (20 mg and 40 mg) and matching placebo. DFD-29 is available for clinical trial use in the form of oral capsules. Placebo for DFD-29 is available as capsules matching DFD-29, formulated with the same excipients, but without minocycline hydrochloride. Oraycea<sup>®</sup> capsules are commercially available and will be purchased by ABF. In order to maintain double blinding of all treatments, ‘over-encapsulation’ (enclosing the original capsule within a second larger capsule shell) will be performed. The identity of the study drug DFD-29 is given in Table 4. The identity of the placebo is given in Table 5 and the identity of Oraycea<sup>®</sup> is given in Table 6.

**Table 4: Identity of Investigational Medical Products**

	Test treatment
Name:	DFD-29 (minocycline HCl) Extended Release Capsules
Active ingredient:	minocycline HCl
Formulation:	Extended Release Capsules
Dose strength:	20 mg or 40 mg minocycline
Dose:	1 capsule
Posology:	1-0-0 (once daily, in the morning)
Mode of administration:	Oral administration with approx. 240 mL water
Administration condition:	Fasting state preferred, but not mandatory
Duration of administration:	16 weeks
Batch number & Expiry date:	Will be given in the TMF ***.

\*\*\* The documentation allowing traceability will be provided in the TMF.

**Table 5: Identity of Placebo**

	Test treatment
Name:	Placebo for DFD-29
Active ingredient:	Not applicable
Formulation:	Capsules
Dose strength:	Not applicable
Dose:	1 capsule
Posology:	1-0-0 (once daily, in the morning)
Mode of administration:	Oral administration with approx. 240 mL water
Administration condition:	Fasting state preferred, but not mandatory
Duration of administration:	16 weeks
Batch number & Expiry date:	Will be given in the TMF ***.

\*\*\* The documentation allowing traceability will be provided in the TMF.

**Table 6: Identity of Oraycea<sup>®</sup>**

	Test treatment
Name:	Oraycea <sup>®</sup>
Active ingredient:	Doxycycline monohydrate
Formulation:	Capsule with 30 mg immediate release and 10 mg delayed release beads
Dose strength:	40 mg doxycycline
Dose:	1 capsule
Posology:	1-0-0 (once daily, in the morning)
Mode of administration:	Oral administration with approx. 240 mL water
Administration condition:	Fasting state preferred, but not mandatory
Duration of administration:	16 weeks
Batch number & Expiry date:	Will be given in the TMF ***.

\*\*\* The documentation allowing traceability will be provided in the TMF.

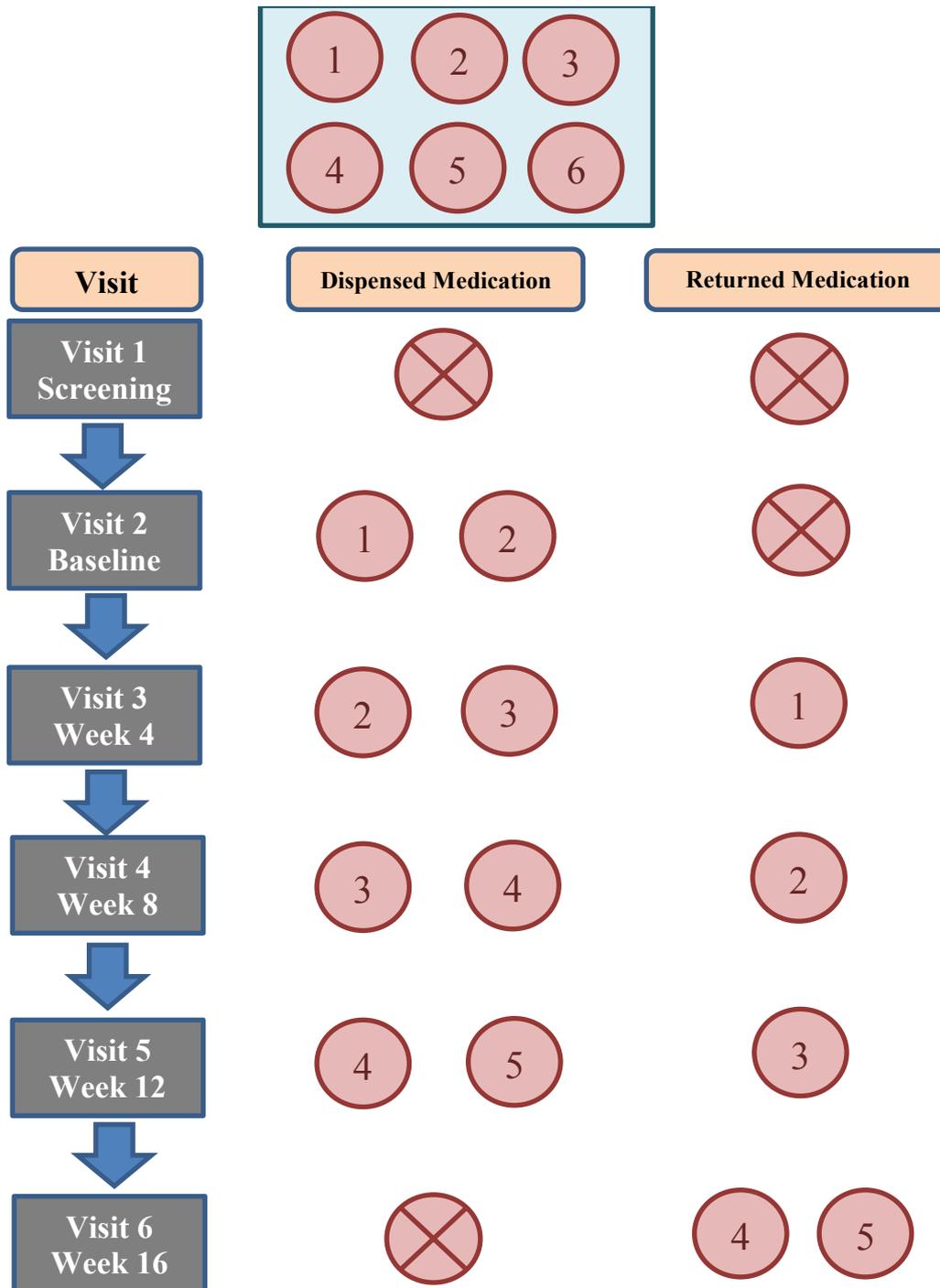
### **8.3.2 Study Drug Supply and Packaging**

DFD-29 (minocycline HCl) Extended Release Capsules and placebo for DFD-29 will be supplied by Dr. Reddy's Laboratories as 25 count in HDPE bottle. The study drug will be imported by QPS and further managed by ABF.

The study drugs will be supplied to ABF where over-encapsulation, re-packaging and the clinical labeling will be performed. Over-encapsulation will be performed with DFD-29, placebo and Oraycea<sup>®</sup> capsules in order to achieve double blinding of formulations. Subsequently, the capsules will be re-packed into new HDPE bottles (of specifications identical to the one in which stability of DFD-29 capsules has been evaluated) containing 25 capsules. The medication bottles will be labeled according to ABF's procedure as stated in Section 8.3.3 See sample label [Figure 8-2](#).

The clinical labelled study drug will be supplied to the investigational sites in HDPE bottle packs of 25 units. Boxes containing 6 bottles of each strength of DFD-29 (minocycline HCl) Extended Release Capsules (20 mg and 40 mg), Oraycea<sup>®</sup> (doxycycline) Modified Release Hard Capsules and placebo will be provided as individual subject kits. The six bottles in each individual subject kit are numbered consecutively. From the kit, two consecutively numbered bottles will be provided to the subjects during visits 2-5, starting with the lowest number available. Subjects will be instructed to always take the capsules from the bottle with the lowest number, until the same is empty and then start with the other bottle. Both bottles received by a subject during a visit, whether unused, partially used or empty, must be returned to the study staff at the successive visit. The study staff will verify the accountability of the IMPs. Partially used bottles will be re-dispensed at the successive visit, while emptied bottles will be replaced with the next bottle from the kit bearing the lowest available number (see [Figure 8-1](#)).

**Figure 8-1: Flowchart for dispensing and returning of study medication**



**Bottle Number 6 is a reserve bottle!**

### 8.3.3 Study Drug Labeling

The labeling complies with the applicable (local) laws and regulations. The labels will be in German language. An English version will be available for review purposes. At the minimum, the following information will be provided on the label:

- Study number (DFD-29-CD-002)
- Study drug (25x DFD-29, 20 mg / 40 mg / placebo / Oraycea<sup>®</sup> Capsules)
- Name, address and telephone number of sponsor or CRO
- Batch number
- Subject identification/treatment number
- Bottle number
- Quantity of dosage units
- Route of administration (e.g., oral)
- Directions for use
- Storage conditions
- Retest or expiry date
- “For clinical trial use only” or similar cautionary statement
- “Keep out of reach of children” or similar cautionary statement

Study drugs might be relabeled during the trial. A possible reason for relabeling might be an extension of the expiry period which is stated on the clinical label. Any relabeling activities will be coordinated by QPS. Relabeling activities will be done according to a re-labeling protocol and will be documented accordingly. A Qualified Person (QP) will be responsible for final release of the investigational medicinal products for use in the trial. Final labeling activities including the stated re-test date on the products are part of the approval by the QP.

## Figure 8-2: Sample Label

**Bottle Label Text**

Prüfplancode: DFD-29-CD-002

EudraCT Nr.: 2016-003197-41

Sponsor: Dr. Reddy's Laboratories Ltd., India; 8-2-337, Road No. 3, Banjara Hills, Hyderabad; Telangana 500034, India; Tel.: 00-91-4434-6126

CRO: QPS Austria GmbH; Parkring 12; 8074 Grambach, Austria; Tel.:+43 316 258 111

Inhalt: 25 Kapseln 20 mg Minocyclin oder 40 mg Minocyclin oder 40 mg Oraycea oder Placebo zur oralen Anwendung

Nach Anweisung des Prüfarztes anwenden.

Lagerung bei 25 °C. Temperaturabweichungen zwischen 15 °C – 30 °C sind erlaubt.

Für Kinder unzugänglich aufbewahren.

Nur zur klinischen Prüfung bestimmt.

Geöffnete Flaschen sind innerhalb von 30 Tagen zu verbrauchen.

Nicht verbrauchte Kapseln und leere Flaschen sind bei jedem Studienbesuch zurückzugeben.

Ch.-B.: XXXXX

Verwendbar bis: MM/YYYY

Kitnr.: XXXX

Flaschennr.: [X] X = 1 oder 2 oder 3 oder 4 oder 5 oder 6

Patientennr.: \_\_\_\_\_

**Box Label Text**

Prüfplancode: DFD-29-CD-002

EudraCT Nr.: 2016-003197-41

Sponsor: Dr. Reddy's Laboratories Ltd., India; 8-2-337, Road No. 3, Banjara Hills, Hyderabad; Telangana 500034, India; Tel.: 00-91-4434-6126

CRO: QPS Austria GmbH; Parkring 12; 8074 Grambach, Austria; Tel.:+43 316 258 111

Inhalt: 6 Flaschen zu je 25 Kapseln 20 mg Minocyclin oder 40 mg Minocyclin oder 40 mg Oraycea oder Placebo zur oralen Anwendung

Nach Anweisung des Prüfarztes anwenden.

Lagerung bei 25 °C. Temperaturabweichungen zwischen 15 °C – 30 °C sind erlaubt.

Für Kinder unzugänglich aufbewahren.

Nur zur klinischen Prüfung bestimmt.

Geöffnete Flaschen sind innerhalb von 30 Tagen zu verbrauchen.

Nicht verbrauchte Kapseln und leere Flaschen sind bei jedem Studienbesuch zurückzugeben.

Ch.-B.: XXXXX

Verwendbar bis: MM/YYYY

Kitnr.: XXXX

Patientennr.: \_\_\_\_\_

### **8.3.4 Study Drug Administration**

The Investigational product will be taken at a fixed time of the day once a day ( $\pm 2$  hours), for 16 consecutive weeks. The preferred time of administration of the study drug will be in the morning, after an overnight fast. One capsule of the assigned study drug will be swallowed with 240 mL (1 glass) of still water on an empty stomach. For dietary aspects upon study drug administration please refer to Section 8.2.3.2.

### **8.3.5 Drug Accountability**

The study drug bottles will have to be returned at each scheduled visit. The investigator will count the number of capsules remaining in the returned bottles and document it in the drug accountability form.

At the initiation visit of the study the site will receive drug accountability forms to document dispensing and returning of study medication. These forms will be made available to the authorized persons (e.g. Clinical Monitor, Auditor) and will include the following information: study number, dates, quantities, batch number and subject randomization number. A drug supply inspection for inventory purposes and to ensure proper storage will be conducted at regular intervals throughout the study.

### **8.3.6 Storage and Return of Study Drug**

Upon receipt of the study drugs at the site, all study drugs will be inspected for completeness. Subsequently, the recipient must immediately return the enclosed acknowledgement of receipt form duly completed and signed (the date of receipt must be noted).

The Investigator or delegate is responsible for storage of the study drug at the study site in an appropriate lockable room at the correct storage conditions which will be described in the pharmacy manual.

All unused investigational material (drugs and packaging) must be returned to ABF on termination of the study and after a drug accountability check by the monitor where it will be destroyed.

The Investigator or delegate of each site will be responsible for the inventory and accountability of the clinical supplies provided to that site, exercising accepted pharmaceutical practices. An accurate, timely record of the clinical study supply will be maintained. The original Drug Accountability Record is considered as source data and will be archived at the site.

## **8.4 Study Drug Discontinuation and Study Withdrawal**

### **8.4.1 Study Drug Interruption or Discontinuation**

The investigator must temporally interrupt or permanently discontinue the study drug if continued administration of the study drug is believed to be contrary to the best interests of the subject. The interruption or premature discontinuation of study drug might be triggered by:

- An adverse event
- A diagnostic or therapeutic procedure
- An abnormal assessment (e.g. vital signs or laboratory abnormalities)

- Administrative reasons, in particular withdrawal of the subject's consent, or subject becomes uncooperative.

The reason for study drug interruption or premature discontinuation must be documented in the eCRF and the sponsor must be informed. If the reason for discontinuation from study drug is an abnormal result on a laboratory test or vital sign this information will be recorded as an AE in the eCRF. The subject will remain under the supervision of the investigator until satisfactory health has returned.

Subjects with protocol deviations should not be withdrawn automatically unless there is a safety concern. The protocol deviation should be recorded in the subject's case record form and Sponsor Consultation Form and included in the study report.

Violations of in- /exclusion criteria lead to discontinuation unless agreed upon otherwise by the sponsor and the investigator, if there is no safety concern.

As far as is possible, Investigators must advise subjects to refrain from consuming the prohibited medication (as specified in [Table 3](#)). In case subject consumes a prohibited concomitant medication or needs to take one, a joint decision will be taken by the medical monitor and Sponsor medical monitor on whether or not the subject should continue in the study or be withdrawn, depending upon the potential for harmful drug-drug interaction and influence on study efficacy assessments. The Investigator must communicate information about the study drug taken/ required by subject, including its generic name, dose and duration of treatment and reason for subject taking/ being advised to take the drug, as soon as it comes to his/her knowledge, to QPS clinical study coordinator, who in turn should forward the information to QPS and Sponsor medical monitors for a decision on continuation of the subject to be taken.

Subjects who experience an AE resulting in or requiring discontinuation of study product use should be encouraged to be followed up in the study until the AE is resolved or stabilized.

Subjects whose treatment randomization is unblinded at the study site should stop the study treatment immediately and be withdrawn from the study after follow-up.

If a female subject becomes pregnant during the study, the study product will be discontinued immediately and she will be followed through the pregnancy and delivery. Details of the pregnancy, delivery and health of the infant should be recorded on the Pregnancy Report Form and the sponsor should be notified immediately.

#### **8.4.2 Study Discontinuation**

Subjects may prematurely discontinue the study at any time. However, subjects are requested to come back for an EOS examination for safety reasons.

Premature discontinuation from the study is to be understood as:

- Subject did not undergo the EOS examination and/or
- Subject is missing pivotal efficacy assessments

Generally, subjects will be withdrawn from the study if any of the following occurs during the study period, i.e. from Screening Visit to end of study (EOS):

- Screening failure
- Lost to follow-up

- Subject who decides to withdraw their informed consent
- Subject has used prohibited treatments as listed in the Section 8.2.3 as confirmed by QPS and Sponsor medical monitor.
- Any pathological event, clinical adverse event, or any change in the subject's status giving indication to the investigator that further participation in the study may not be the best interest of the subject
- Subject develops an exclusion criterion and is no longer eligible to continue in the study
- Subject is lacking the interest, understanding, desired compliance and willingness to adhere to follow study procedures or adhere to restrictions to continue with the trial
- Administrative Reasons
- If a female subject becomes pregnant during the study, study product will be discontinued immediately and she will be followed through the pregnancy and delivery. Details of the pregnancy, delivery and health of the infant should be recorded on the Pregnancy Report Form and the sponsor notified immediately.

A subject will be considered as 'lost to Follow-up' if, and only if, he/she cannot be reached after exhausting all means of contact. Every attempt should be made to contact subjects who are lost-to-follow-up for a final safety assessment. At least three attempts must be documented in the subject's source document including the use of at least 1 certified letter. Any contact, either direct or indirect, should be made with the purpose to document the final status of the subject with regard to safety.

Subjects who are withdrawn due to adverse event(s) or serious adverse event(s) should be followed until resolution or until the event is considered stable.

The reasons for premature discontinuation of the study must be documented in the eCRF and the sponsor must be informed.

Drop-outs will not be replaced.

#### **8.4.3 Subject's Follow-up after Study Discontinuation**

Included subjects can leave the study at any time for any reason if they wish to do so, without any consequences.

In the case of premature discontinuation after study drug intake, the assessments scheduled for the EOS examination will be performed as soon as possible.

For terms and conditions of early termination of this study please refer to Section 11.1.9.

### **8.5 Treatment Exposure and Compliance**

Study drug accountability is performed at each scheduled visit by the study staff and checked by the monitor during site visits and at the completion of the study.

Concerning missed doses: In case 6 or less consecutive doses are missed, subjects may continue with the study medication. If 7 or more consecutive doses are missed withdrawal from the study has to be considered by the investigator in agreement with the sponsor. The subject has to be at least 80% to 120% drug compliant (overall) to be analyzed per protocol (e.g. the subject should have received between 90 to 135 single doses of the assigned IP over 16 weeks).

## 8.6 Treatment Assignment and Blinding

### 8.6.1 Assignment of Subject Numbers

Subjects will receive a number on Day 1 before start of procedures/assessments. The assignment of number and code for subject identification is based on the obligation for anonymity.

During Screening, the sites will assign three-digit sequential subject numbers preceded by a site number (e.g. 01-001). Upon inclusion into the study, the subjects will receive a four-digit randomization number (kit code) which does not contain site identification.

### 8.6.2 Treatment Assignment

Subjects will be randomized to any of the treatments assigned in a 1:1:1:1 fashion. Block size will be determined by the statistician of QPS Netherlands. Randomization will be stratified per site. The first randomizations (approximately 40% of the patients) were also stratified per IGA score. This stratification resulted in a high amount of study medication kits to be stored at the site, limiting the overall availability of unexpired kits in the study. Therefore stratification per IGA score is dropped and randomization is only stratified per site at Baseline. In order to achieve a patient population in the study with adequate representation of patients with moderate to severe illness (IGA score above 2) not more than 20 % of enrollments in the study will be of IGA grade 2 at Baseline.

The randomization code will be generated by a computer program (OpenClinica) and is stored securely. It is accessible only to authorized persons who are not involved in the conduct and analysis of the study, until time of un-blinding.

Randomization is controlled by the study drug packaging. The number on the subject kit equals the randomization number. The kits will be allocated to the sites.

Randomization will be performed by the validated randomization module of OpenClinica. This module uses the randomization from Sealed Envelope™. Subjects will be assigned to a kit code (matching the randomization number).

The randomization number will be un-blinded and made available for data analysis only after study closure, i.e., when the study has been completed, the protocol deviations determined and the clinical database declared complete, accurate, and locked.

### 8.6.3 Double-blinding

The study is performed in a double-blind fashion. The investigator and study staff (including lab personnel), the subjects, the monitors, medical monitors, the CRO personnel involved in clinical operations and the sponsor's staff will remain blinded to the treatment until study closure. The investigational product and its matching placebo and active comparator (Oraycea®) are indistinguishable after over-encapsulation, and all subject bottles will be packaged and labelled in the same way.

The randomization code will be kept strictly confidential. It is accessible only to authorized personnel, who are not involved in the conduct and analysis of the study, and will keep the randomization scheme strictly confidential.

#### **8.6.4 Emergency Procedure for Unblinding**

The investigator has access to emergency envelopes for each subject containing the identity of the study drug dispensed. The investigator and the study staff must remain blinded to the subject's treatment assignment, even if the subject refuses to participate in any study procedures or experiences an AE. The identity of the study drug may be revealed only if the subject experiences a medical emergency whose management would be improved by the knowledge of the blinded treatment assignment. Subjects who have thus been unblinded prematurely will be discontinued from the study.

The occurrence of any code break during the study must be clearly justified and explained by the investigator. Before accessing the emergency envelope, every attempt must be made by the investigator to discuss the intended code break with the study monitor and Dr. Reddy's. In all cases, the sponsor must be informed as soon as possible before or after the code break.

Every code break must be documented.

### **8.7 Study Parameters**

#### **8.7.1 Efficacy Endpoints**

The following parameters have been defined as parameters regarding efficacy. Treatment success is achieved only if both primary endpoints are met. Baseline is defined as the last value measured prior to the first intake of assigned study drug.

##### **Co-Primary endpoints:**

- Proportion of subjects with IGA (modified scale without erythema) 'treatment success' – Grade 0 or 1 at the end of study with at least 2 grade reduction from Baseline to Week 16.
- Total inflammatory lesion count (sum of papules, pustules, and nodules) reduction from Baseline to Week 16.

##### **Secondary endpoints**

- Proportion of subjects with at least a 2 grade reduction in IGA (modified scale without erythema) score from Baseline to Week 16
- Median change in total RosaQoL score from Baseline to Week 16.

##### **Exploratory endpoints**

- Proportion of subjects with IGA (modified scale without erythema) 'treatment success' from Baseline to Weeks 4, 8 and 12.
- Total inflammatory lesion count (sum of papules, pustules, and nodules) reduction from Baseline to Weeks 4, 8 and 12.
- Proportion of subjects with at least a 2 grade reduction in IGA (modified scale without erythema) score from Baseline to Week 4, 8 and 12.
- Median change in total RosaQoL score from Baseline to Weeks 4, 8 and 12.
- Mean change in high sensitivity C-reactive protein (hs-CRP) levels from Baseline compared to Week 16.
- Change in Telangiectasia score from Baseline compared to Week 16.
- Proportion of subjects meeting CEA 'treatment success' criteria (i.e. a two grade improvement in the CEA scale) at Weeks 4, 8, 12 and 16

### **8.7.2 Safety and Tolerability Endpoints**

Baseline is defined as the last value measured prior to the first DFD-29 intake (vital signs, laboratory parameters). Please refer to Sections [8.1.2](#) and [8.1.3](#) for activities performed during individual, study visits.

The following parameters have been defined as parameters regarding safety and tolerability:

- Change from Baseline to each scheduled time point up to EOS for vital signs.
- Change from Screening up to EOS for physical examination.
- Change from Screening up to EOS for clinical laboratory tests.
- Treatment-emergent AEs up to EOS.
- Treatment-emergent AEs leading to premature discontinuation of study drug.
- Treatment-emergent SAEs up to EOS.

For pre-existing conditions, any event that worsens during treatment will be considered treatment-emergent.

## 9 SAFETY DEFINITIONS AND REPORTING REQUIREMENTS

### 9.1 Adverse Events

#### 9.1.1 Definitions of Adverse Events

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (see the ICH guidance for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

A treatment-emergent AE is any AE temporally associated with the use of a study drug, whether or not considered related to the study drug.

Adverse events will be collected by spontaneous reports from subjects, either verbal or recorded in the subject's diary, by directed question of subjects, and by observation. All AEs from the time of signing of the ICF up to the EOS visit will be recorded.

Adverse events include:

- Exacerbation of a pre-existing disease.
- Increase in frequency or intensity of a pre-existing episodic disease or medical condition.
- Disease or medical condition detected or diagnosed after study drug administration even though it may have been present prior to the start of the study.
- Continuous persistent disease or symptoms present at Baseline that worsen following the start of the study.
- Events considered by the investigator to be related to study-mandated procedures.
- Abnormal assessments, e.g. vital signs or physical examination findings, must be reported as AEs if they represent a clinically significant finding that was not present at Baseline or worsened during the course of the study.
- Laboratory test abnormalities must be reported as AEs if they represent a clinically significant finding, symptomatic or not, which was not present at Baseline or worsened during the course of the study or led to dose reduction, interruption or permanent discontinuation of study drug.

Adverse events do not include:

- Medical or surgical procedure, e.g., surgery, endoscopy, tooth extraction, transfusion. However, the event leading to the procedure is an AE. If this event is serious, the procedure must be described in the SAE narrative.
- Pre-existing disease or medical condition that does not worsen.
- Situations in which an adverse change has not occurred, e.g., hospitalizations for cosmetic elective surgery or for social and/or convenience reasons.
- Overdose of either study drug or concomitant medication without any signs or symptoms. However, overdose must be mentioned in the Study Drug Log.

### 9.1.2 Intensity of Adverse Events

The intensity of clinical AEs is graded on a three-point scale: mild, moderate, severe, and reported on specific AE pages of the eCRF.

If the intensity of an AE worsens during study drug administration, the AE will be closed and a new AE with enhanced severity will be generated in the eCRF. If the AE lessens in intensity, no change in the severity is required.

If an AE occurs during a washout or placebo run-in phase and afterwards worsens during the treatment phase, a new AE page must be filled in with the intensity observed during study drug administration.

**Mild:** Event may be noticeable to subject; does not influence daily activities; usually does not require intervention.

**Moderate:** Event may make subject uncomfortable; performance of daily activities may be influenced; intervention may be needed.

**Severe:** Event may cause noticeable discomfort; usually interferes with daily activities; subject may not be able to continue in the study; treatment or intervention is usually needed.

A mild, moderate or severe AE may or may not be serious. These terms are used to describe the intensity of a specific event (as in mild, moderate, or severe myocardial infarction). However, a severe event may be of relatively minor medical significance (such as severe headache) and is not necessarily serious. For example, nausea lasting several hours may be rated as severe, but may not be clinically serious. Fever of 39 °C that is not considered severe may become serious if it prolongs hospital discharge by a day (see Section 9.2.1.2). Seriousness rather than severity serves as a guide for defining regulatory reporting obligations.

These definitions do not apply to clinically significant and asymptomatic laboratory test abnormalities or abnormal assessments considered as AEs. The investigator should tick non-applicable on the AE page of the eCRF to qualify the intensity of the AE.

### 9.1.3 Relationship to Study Drug

Adverse events should be assessed by the investigators as to whether or not there is a reasonable possibility of causal relationship to the study drug and reported as either definite, probable, possible, , not related, as defined below:

1. **Not Related:** The event is clearly due to extraneous causes (e.g., diseases, environment, etc.). Specify if known. Or, the event is most probably produced by other factors such as the subject's clinical state, therapeutic interventions, or concomitant therapy and does not follow a known response pattern to the study product.
2. **Possibly Related:** The event is temporally related to study product use but can be explained by another etiology. Information on the effect of study product withdrawal may be lacking.

3. Probably Related: The event is temporally related to study product use and is consistent with known effects of the study product and/or improves upon withdrawal of the study product.
4. Definitely Related: The event follows a reasonable temporal sequence from the time of study product administration and/or follows a known response pattern to the study product, and could not have been produced by other factors such as the subject's clinical state, therapeutic intervention, or concomitant therapy, and either occurs immediately following study product administration or improves on stopping the product, or there is a positive reaction at the application site.

#### 9.1.4 Reporting of Adverse Events

All AEs occurring after signing the informed consent form and until EOS must be recorded on specific AE pages of the eCRF. If the investigator becomes aware of a new AE up to 30 days after EOS visit, it is within his discretion to follow up the AE and document appropriately.

#### 9.1.5 Follow-up of Adverse Events

All subjects experiencing AEs (whether considered associated with the use of the study drug or not) must be monitored until:

- resolution of AE
- stabilization of AE
- subject is lost to follow up
- death of subject
- or until the investigator considers it medically justifiable to terminate the follow-up

## 9.2 Serious Adverse Events

### 9.2.1 Definitions

#### 9.2.1.1 Serious Adverse Events

A Serious Adverse Event (SAE) is defined by the International Conference on Harmonization (ICH) guidelines as any AE fulfilling at least one of the following criteria:

- Fatal.
- Life-threatening.
- Requiring subject's hospitalization or prolongation of existing hospitalization.
- Resulting in persistent or significant disability or incapacity.
- Congenital anomaly or birth defect.
- Medically significant or requires intervention to prevent at least one of the outcomes listed above.
- Life-threatening refers to an event in which the subject was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
- Important medical events that may not immediately result in death, be life-threatening, or require hospitalization may be considered as SAEs when, based upon appropriate medical judgment, they may jeopardize the subject and may require

medical or surgical intervention to prevent one of the outcomes listed in the definitions above.

The reference safety document to assess whether or not an SAE should be reported by the sponsor to Health Authorities, ECs/IRBs and investigators in an expedited fashion is the Investigator's Brochure.

#### 9.2.1.2 Hospitalization - Prolongation of Existing Hospitalization

Hospitalization is defined as an overnight stay in a hospital unit and/or emergency room.

An additional overnight stay defines a prolongation of existing hospitalization.

The following is not considered an SAE and should be reported as an AE only:

- Treatment on an emergency or outsubject basis for an event not fulfilling the definition of seriousness given above and not resulting in hospitalization.

The following reasons for hospitalizations are not considered AEs, and therefore not SAEs:

- Hospitalizations for cosmetic elective surgery, social and/or convenience reasons.
- Standard monitoring of a pre-existing disease or medical condition that did not worsen, e.g., hospitalization for coronary angiography in a subject with stable angina pectoris.
- Elective treatment of a pre-existing disease or medical condition that did not worsen, e.g., hospitalization for chemotherapy for cancer, elective hip replacement for arthritis.

#### 9.2.1.3 Serious Adverse Events Related to Study-mandated Procedures

Such SAEs are defined as SAEs that appear to have a reasonable possibility of causal relationship (i.e., a relationship cannot be ruled out) to study-mandated procedures (excluding administration of study drug) such as discontinuation of subject's previous treatment during a washout period, or complication of a mandated invasive procedure (e.g., blood sampling, heart catheterization), or car accident on the way to the hospital for a study visit, etc.

### **9.2.2 Reporting of Serious Adverse Events**

Detailed reporting procedures will be described in a separate Safety Management Plan, and are shortly outlined below.

#### 9.2.2.1 Before Study Drug Initiation

Serious adverse events occurring after signature of the Informed Consent and up to study drug initiation must be reported to Dr. Reddy's Laboratories Ltd, Clinical Pharmacovigilance only if they are considered by the investigator to be related to study-mandated procedures.

#### 9.2.2.2 During Study Drug Administration

All SAEs regardless of causal relationship must be reported, including those related to study-mandated procedures. These SAEs occurring during study drug administration, i.e., between study drug initiation and EOS after study drug discontinuation, are defined as treatment emergent SAEs.

These SAEs are reported on SAE forms and also on AE pages in the eCRF. Therefore, they are entered both in the drug safety and clinical databases, and must be reconciled before study closure.

#### 9.2.2.3 After Study Drug Discontinuation

New SAEs, including those related to study-mandated procedures, occurring during study drug administration, i.e., between study drug initiation and EOS, must be reported.

All SAEs occurring up to 30 days after study drug discontinuation must be recorded on an SAE form and as AEs in the eCRF. Therefore, these treatment-emergent SAEs are entered both in the drug safety and clinical databases, and must be reconciled before study closure.

#### 9.2.2.4 Reporting Procedures

All SAEs must be reported by the investigator to Dr. Reddy's Laboratories Ltd, Clinical Pharmacovigilance, the Sponsor Medical Monitor, and the QPS Medical Monitor within 24 hours of the investigator's knowledge of the event.

All SAEs must be recorded on SAE forms, irrespective of the study drug received by the subject, whether or not this event is considered by the investigator to be related to study drug.

These SAE forms must be faxed or send via E-mail to Dr. Reddy's Laboratories Ltd, Clinical Pharmacovigilance and the QPS Medical Monitor. The investigator must complete the SAE form in English (unless otherwise specified) and assess the relationship to study drug.

Contact details are provided below:

Dr. Reddy's Laboratories Ltd, Clinical Pharmacovigilance:  
Shahida Hasan, MD  
Associate Director  
Fax: +1 908-450-1510 / +1 877-445-3741  
Email: sae@drreddys.com

Dr. Reddy's Laboratories Ltd, Medical Monitor:  
Dr. Srinivas Shenoy B., MBBS, MD  
Principal Scientist- Clinical Studies  
Tel No.: +91-40-4434 6126 (Direct)  
E-mail: srinivasshenoyb@drreddys.com

QPS, Medical Monitor:  
Antón Alvarez, MD, PhD  
Country and Clinical Research Director QPS Holdings, LLC  
Phone +34 981 236718  
Mobile +34 629014472  
Fax +34 881 090633  
Email: anton.alvarez@qps.com

Such preliminary reports will be followed by detailed descriptions that should include copies of hospital case reports, autopsy reports, hospital discharge summaries and other documents when requested and applicable. Follow-up information about a previously reported SAE must also be reported within 24 hours of receiving it. The Sponsor's Pharmacovigilance department may contact the investigator to obtain further information.

Suspected (considered related to the study drug) and Unexpected (not previously described in the reference safety document), Serious Adverse Reactions (SUSARs) will be expedited by the Sponsor's Pharmacovigilance department to Health Authorities, ECs/IRBs, as appropriate. All SAEs judged to be SUSARs and reportable will be unblinded. SUSAR related unblinding will be performed by the Sponsor's Pharmacovigilance department as outlined within the Safety Management Plan. QPS will be responsible for sending blinded reports to the Investigators.

### **9.2.1 Follow-up of Serious Adverse Events**

Serious adverse events still ongoing at the End-of-Study visit must be followed until resolution or stabilization or until the event is otherwise explained.

New SAEs occurring at any time after the 30-day follow-up period after study drug discontinuation (whichever comes first) may be reported to Dr. Reddy's Laboratories Ltd, Clinical Pharmacovigilance within 24 hours of the investigator's knowledge of the event, if felt appropriate by the investigators.

Such information will only be entered into the drug safety database and hence will not affect study closure.

### 9.3 Pregnancies

All subjects will be instructed to use adequate contraceptive precautions. When pregnancy of a subject or a subject's spouse has been discovered, the pregnancy must be recorded on a pregnancy reporting form and reported to Dr. Reddy's Laboratories Ltd, Clinical Pharmacovigilance and the QPS Medical Monitor. The pregnancy outcomes, including spontaneous or voluntary termination, details of the pregnancy and birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications, will be followed. The infant's medical record should be followed up to 1 year after birth.

## 10 STATISTICAL METHODOLOGY AND ANALYSES

### 10.1 Statistical Analysis Plan

A statistical analysis plan (SAP) will be written and finalized by QPS before the study closure, i.e., database closure and unblinding of the randomization code of the study. The SAP will provide full details of the analyses, level of significance to be used, the data displays and the algorithms to be used for data derivations. Furthermore, the number of subjects planned to be enrolled is given in the SAP. The SAP will include the definition of major and minor protocol deviations/violations and the link of major protocol deviations/violations to the analysis sets.

### 10.2 Analysis Populations

Four different analysis sets are defined. Subjects who withdraw from the study, or who have missing data, will be included in the statistical analyses provided that they are eligible for inclusion in the analysis population as described below.

**Full analysis set (FAS):** This analysis population includes all subjects who have been randomized and had at least one post baseline efficacy assessment. The FAS population will be the primary population for the efficacy analyses.

**Intention to treat population (ITT):** This analysis population includes all subjects who have been randomized and dispensed the study drug.

**Safety population:** This analysis population includes subjects who had at least one safety assessment post-baseline. The safety population will be employed in the analysis of tolerability and safety variables.

**Per-protocol population (PP):** This analysis population comprises all subjects who did not violate the protocol in a way that might affect the evaluation of the effect of the study drug(s) on the primary endpoint, i.e., without major protocol violations or deviations.

#### 10.2.1 Sample Size

On the basis of comparable pharmacokinetic parameters of orally administered minocycline hydrochloride to doxycycline, it is assumed that DFD-29 (minocycline hydrochloride) will demonstrate an efficacy either similar or better than that reported with ORACEA<sup>®</sup> (doxycycline) 40 mg in the treatment of inflammatory lesions of papulopustular rosacea. The sizes of the treatment effect of doxycycline 40 mg in comparison to placebo that were reported from the two pivotal efficacy and safety clinical trials, that formed the basis of approval of ORACEA<sup>®</sup> (by USFDA, [see review](#)) for the treatment of only inflammatory lesions of rosacea, in terms of the two co-primary endpoints in this study, are presented in brief in the [Table 7](#) below.

**Table 7: Efficacy of Oracea<sup>®\*</sup> 40 mg/day as shown in two phase 3 trials**

	Study 1		Study 2	
	Oracea <sup>®</sup> N=127	Placebo N=124	Oracea <sup>®</sup> N=142	Placebo N=144
Mean change in lesion counts from Baseline	-11.82 ±9.78	-5.94 ± 13.91	-9.48 ± 9.63	-4.31 ± 11.57
Proportion of subjects with IGA of '0' or '1' at the end of study	39 (30.7%)	24 (19.4%)	21 (14.8%)	9 (6.3%)

\*US American trade name

Using the more conservative estimate of the difference in the treatment means of 5.17 lesions (from Study 2) and the estimated population variance of 112, the sample size required is calculated to be 44 subjects per group to achieve 70% power in the study. By accounting for an expected subject discontinuation rate of 10%, the required sample size is rounded of to 50 subjects per group.

The above determined sample size of 44 subjects per treatment group was also seen to ensure an adequately powered analysis (87%) for demonstrating non-inferiority of DFD-29 40 mg and DFD-29 20 mg treatments against the active comparator Oracea<sup>®</sup> while assuming the lower limit of the 90% CI for concluding non-inferiority to be  $\leq 3$  for the absolute change in total inflammatory lesion count from Baseline at Week 16 for the individual DFD-29 treatment arms versus Oracea<sup>®</sup> arm, a common standard deviation of 5 lesion counts, the expected difference of treatment means to be 0 and alpha of 0.05 (one sided). Similarly, this sample size will also achieve 91% power to detect a non-inferiority margin difference of 0.5 points on the RosaQoL, assuming a common standard deviation of 0.77 points.

### 10.2.2 Handling of Missing Data

All safety analyses will be performed on data available at the time point considered. In summary tables, the number of subjects with missing data will be presented unless otherwise specified. In calculation of percentages, subjects with missing data will not be considered in numerator or denominator unless otherwise specified.

For the efficacy data; in case of missing measurements, multiple imputation (MI) will be used to impute the missing values. For the MI of the inflammatory lesion count test and CRP, a MIXED model will be used, with visit as a factor and subject as random variable. For success rate, a logistic model will be used.

## 10.3 Efficacy Parameters

### 10.3.1 Statistical Analysis of Efficacy Parameters

#### Efficacy

For all endpoints, the comparison of oral DFD-29 (40 mg capsule) versus placebo will be the primary objective of the study. All other comparisons viz, between oral DFD-29 (20 mg capsule) and placebo, between oral DFD-29 (40 and 20 mg capsules) and Oracea<sup>®</sup> and between oral DFD-29 40 mg capsules and DFD-29 20 mg capsules, will be treated as secondary.

**Co-Primary Endpoints**

- The proportion of subjects with IGA (modified scale without erythema) ‘treatment success’ – will be investigated with a Chi-square test. ‘Treatment success’ is described as having at least 2 grade reduction from Baseline with grade 0 or 1 at Week 16.
- The difference between the treatments in terms of the change from Baseline in the total inflammatory lesion count at Week 16 will be tested using MIXED Model, with the investigator as a random factor.

**Secondary Endpoints:**

- The proportion of subjects with at least a 2 grade reduction in IGA (modified scale without erythema) score from Baseline to Week 16, will be investigated with a Chi-square test.
- Median change in total RosaQoL score from Baseline to Week 16 will be analyzed using ANOVA.

For secondary and exploratory endpoints we assume that non-inferiority would be established if the mean change in inflammatory lesion count in the DFD-29 (40 mg capsule) group would be within 3 less than in the Oraycea<sup>®</sup> group for the lower limit of the 90% Confidence Intervals.

## 10.4 Safety and Tolerability Parameters

Definitions of the safety and tolerability parameters are described in Section 8.7.1.

The safety population is used to perform all safety analyses.

The medical history is coded using the most recent Medical Dictionary for Regulatory Activities (MedDRA) version and listed.

All AEs and SAEs are coded using the most recent MedDRA version at the study start.

The treatment-emergent AEs are tabulated by system organ class (SOC), and individual preferred terms within each SOC by treatment group. The number and percentage of subjects who experienced AEs coded with the same preferred term and SOC will be summarized by treatment group (in descending order according to the incidence in the investigational study drug group). Adverse events will also be tabulated by severity and by relationship to study drug. Summary tables will be accompanied by individual subject listings broken down by treatment group, including pre-dose events.

SAEs will be listed and summarized similarly to AEs.

Reasons for death will only be listed.

Reasons for premature discontinuation of study drug will be listed and summarized by frequency tables.

Individual subject listings of vital signs data and laboratory measurements will be provided. Vital sign measurements and laboratory measurements will be summarized at each time point using mean, median, standard deviation, min, max, number of available observations, and change from Screening or Baseline for the following parameters:

- Change from Baseline to each scheduled time point up to EOS for vital signs compared between DFD-29, Oraycea<sup>®</sup> and placebo.
- Change from Screening up to EOS for physical examination compared between DFD-29, Oraycea<sup>®</sup> and placebo.
- Change from Screening up to EOS for clinical laboratory tests compared between DFD-29, Oraycea<sup>®</sup> and placebo.
- Treatment-emergent AEs up to EOS compared between DFD-29, Oraycea<sup>®</sup> and placebo.
- Treatment-emergent AEs leading to premature discontinuation of study drug compared between DFD-29, Oraycea<sup>®</sup> and placebo.
- Treatment-emergent SAEs up to EOS compared between DFD-29, Oraycea<sup>®</sup> and placebo.

Standard numeric laboratory parameters are presented in the units supplied. If needed, a conversion will be made to standard units.

## 10.5 Exposure to Study Drugs

A listing with information about the drug administration will be provided.

## 10.6 Baseline Parameters and Concomitant Medications

Summary statistics (mean, median, standard deviation, min, max, number of available observations) will be provided for continuous demographic variables (e.g., age, height, weight). Individual subject listings of demographic data will be provided.

Qualitative demographic characteristics (gender, race) will be summarized by counts and percentages. Other Baseline subject characteristics (medical history, physical examination clinical findings, previous medications, inclusion/exclusion checklist) will only be listed.

Distributions of these parameters will be compared between the treatment groups only descriptively. No statistical inference will be performed.

Previous and concomitant medications will be coded by the sponsor according to the World Health Organisation (WHO) drug code and the ATC (Anatomical Therapeutic Chemical) class code. Previous medications will be summarized by tabulating the number and percentages of subjects treated.

## 10.7 Exploratory Analyses

Exploratory data-driven analyses can be performed with the caveat that any statistical inference will not have any confirmatory value.

Exploratory Endpoints:

- Proportion of subjects with at least a two grade improvement of IGA (modified scale without erythema) grade from Baseline to Weeks 4, 8 and 12 will be investigated with a Chi-square test.

- The difference between treatments in terms of the change from Baseline in the total inflammatory lesion count at Weeks 4, 8 and 12 will be tested using MIXED Model with the investigator as a random factor.
- The proportion of subjects with at least a 2 grade reduction in IGA (modified scale without erythema) score from Baseline to Week 4, 8 and 12, will be investigated with a Chi-square test.
- Median change in total RosaQoL score from Baseline to Weeks 4, 8 and 12 will be investigated using ANOVA.
- The difference between treatments will be tested for the mean change in high sensitivity C-reactive protein (hs-CRP) levels from Baseline to Week 16 using ANOVA
- Change in Telangiectasia score from Baseline to Week 16 will be investigated using ANOVA.
- Proportion of subjects meeting CEA ‘treatment success’ criteria (i.e. a two grade improvement in the CEA scale) in the treatment groups at Weeks 4, 8, 12 and 16 will be investigated using ANOVA.

Exploratory analyses for the following subgroups will be performed:

- Male versus female.
- Mild (score 2), moderate (score 3) and severe (score 4) IGA score.
- Normal hs-CRP versus abnormal hs-CRP at Baseline

## 10.8 Clinical Study Report

Safety and tolerability parameters as well as efficacy parameters will be evaluated and the study outcome presented in a Clinical Study Report.

## 11 PROCEDURES AND GOOD CLINICAL PRACTICE

### 11.1 Procedures

#### 11.1.1 Protocol Amendments

Any substantial change to a protocol has to be considered as an amendment as soon as these documents have been submitted to ECs/IRBs or Health Authorities. Therefore, an amendment could occur before or after the approval of these documents by ECs/IRBs or Health Authorities. Each amendment must be documented in writing and approved by Dr. Reddy's. It should be reviewed by the Principal Investigator(s) or Steering Committee, as appropriate.

Adaptations of the core subject Information and Informed Consent requested by ECs/IRBs are not considered as amendments, as long as they do not significantly change the core document or affect the protocol.

##### 11.1.1.1 Non-substantial Amendment

Administrative or logistical minor changes require a non-substantial amendment. Such changes include but are not limited to changes in study staff or contact details (e.g., Dr. Reddy's instead of CRO monitors) or minor changes in the packaging or labeling of study drug.

The implementation of a non-substantial amendment could be done with or without (according to national regulations) notification to the appropriate ECs/IRBs and Health Authorities. It does not require their approval or to be signed by the investigators.

##### 11.1.1.2 Substantial Amendment

Significant changes require a substantial amendment. Significant changes include but are not limited to: new data affecting the safety of subjects, change of the objectives/ parameters of the study, eligibility criteria, dose regimen, study assessments/procedures, treatment or study duration, with or without the need to modify the core Subject Information and Informed Consent.

Substantial amendments are to be approved by the appropriate ECs and in some countries by the Health Authorities. The implementation of a substantial amendment can only occur after formal approval by the appropriate ECs/IRBs and/or Health Authorities and must be signed by the investigators.

##### 11.1.1.3 Urgent Amendment

An urgent amendment might become necessary to preserve the safety of the subjects included in the study. The requirements for approval should in no way prevent any immediate action being taken by the investigators or Dr. Reddy's in the best interests of the subjects. Therefore, if deemed necessary, an investigator can implement an immediate change to the protocol for safety reasons. This means that, exceptionally, the implementation of urgent amendments will occur before submission to and approval by ECs/IRBs and Health Authorities.

In such cases, the investigator must notify Dr. Reddy's within 24 hours. A related substantial amendment will be written within 10 working days by QPS on behalf of Dr. Reddy's and submitted to the appropriate ECs/IRBs and Health Authorities.

### **11.1.2 Monitoring**

The monitor will contact and visit the investigator regularly and will be allowed, on request, to have access to all source documents needed to verify the entries on the eCRF and other protocol related documents; provided that subject confidentiality is maintained in agreement with local regulations. It will be the monitor's responsibility to inspect the eCRF at regular intervals throughout the study, to verify the adherence to the protocol and the completeness, consistency and accuracy of the data being entered on them. Dr. Reddy's monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs and the recording of the main efficacy, safety and tolerability parameters. Additional checks of the consistency of the source data with the eCRFs are performed according to the study-specific monitoring plan.

The investigator must ensure that subjects' anonymity will be maintained. On eCRFs or other documents submitted to Dr. Reddy's, subjects should not be identified by their names, but by the subject number. The investigator must keep a subject identification code list showing the randomization number, the subject's name, date of birth and address or any other locally accepted identifiers. Documents identifying the subjects (e.g., subjects' signed informed consent forms) should not be sent to Dr. Reddy's and must be kept by the investigator in strict confidence.

The investigator and co-investigators agree to cooperate with the monitor(s) to ensure that any issue detected in the course of these monitoring visits is resolved. If the subject is hospitalized or dies in a hospital other than the study center, the investigator is in charge of contacting this hospital in order to document this SAE.

The investigator will supply Dr. Reddy's on request with any required background data from the study documentation or clinic records. This is particularly important when eCRFs are illegible or when errors in data transcription are suspected. In case of special problems and/or governmental queries, it is also necessary to have access to the complete study records, provided that subject confidentiality is protected.

An initiation visit will be performed before the first subject is included. Monitoring visits and contacts will occur at regular intervals thereafter, according to a frequency defined in the study-specific monitoring plan. A close-out visit will be performed after study closure.

### **11.1.3 Data management**

#### **11.1.3.1 Data Collection**

A Subject Screening and Enrollment Log will be completed for all eligible or non-eligible subjects with the reasons for exclusion.

For each subject enrolled, regardless of study drug initiation, an eCRF must be completed and signed by the principal investigator or co-investigator. This also applies to those subjects who fail to complete the study. If a subject withdraws from the study, the reason must be noted on the eCRF. Case report forms are to be completed on an ongoing basis.

Designated investigator staff will enter the data required by the protocol into the electronic Case Report Forms. Designated investigator site staff will not be given access to the EDC system until they have been trained. The Investigator must certify that the data entered into the electronic Case Report Forms are complete and accurate.

#### 11.1.3.2 Database Management and Quality Control

All data from the source documents will be entered into the eCRF if not otherwise stated in this protocol.

The CRA will perform source data verification according to the monitoring plan and the SOPs of the CRS department. The CRA will use the eCRF system to track the monitoring queries and their resolution by the site.

The entered data is systematically checked by Data Management of the CRS department, QPS Netherlands, according to the data validation plan and the applicable SOPs.

After the eCRF has been declared complete and accurate, the eCRF will be locked, after written approval of the Sponsor. Any changes to the eCRF after that time can only be made after receipt of written approval of the Sponsor.

Quality assurance (QA) performs process audits based on their annual audit plan (results are not shared with sponsors). On request of the sponsor, QA may perform a study audit including the data management process.

#### **11.1.4 Recording of Data and Retention of Documents**

The investigator will maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents will be classified into two different categories: investigator's file, and subject clinical source documents.

The investigator's file will contain the protocol/amendments, a copy of the eCRFs and data clarification and query forms (after database lock), EC/IRB and Health Authority approval with correspondence, informed consent, drug records, staff curriculum vitae and authorization forms, screening and enrollment logs, and other appropriate documents/correspondence as per ICH/Good Clinical Practice (GCP) and local regulations.

Subject clinical source documents include, but are not limited to subject hospital/clinic records, physician's and nurse's notes, appointment book, original laboratory reports, pathology and special assessment reports, consultant letters, etc.

These two categories of documents must be kept on file by the investigator for as long as needed to comply with national and international regulations (generally 2 years after discontinuing clinical development or after the last marketing approval). No study document should be destroyed without prior written approval from Dr. Reddy's. Should the investigator wish to assign the study records to another party, or move them to another location, Dr. Reddy's must be notified in advance.

When source documents are required for the continued care of the subject, appropriate copies should be made for storing outside of the site.

#### **11.1.5 Audit**

The Dr. Reddy's Quality team may conduct audits of clinical research activities in accordance with internal standard operating procedures (SOPs) to evaluate compliance with the principles of GCP and ICH related guidelines.

Health Authorities may also wish to conduct an inspection (during the study or after its completion). Should an inspection be requested by Health Authorities, the investigator must inform Dr. Reddy's immediately that such request has been made.

The investigator will permit such audits by Dr. Reddy's or Health Authorities and facilitate them by providing access to the relevant source documents.

#### **11.1.6 Handling of Study Drugs**

ABF will supply all study drug to the site according to local regulations. Drug supplies must be kept in an appropriate, secure area and stored according to the conditions specified on the drug labels. The site must maintain an accurate record of the shipment and dispensing of study drug on an accountability form, which must be given to the monitor at the end of the study. An accurate record of the date and amount of study drug dispensed to each subject must be available for inspection at any time.

All drug supplies are to be used only for this protocol and not for any other purpose. The responsible person must not destroy any drug labels, or unused drug supply. Upon termination of the study, the monitor will collect used and unused drug subject bottles. They will be sent to the warehouse, where the sponsor or its deputy will check drug accountability. In certain circumstances, used and unused drug containers can be destroyed at the site once drug accountability is final and checked by the sponsor or its deputy and written permission for destruction has been obtained from Dr. Reddy's.

#### **11.1.7 Publication of Study Results**

In accordance with standard editorial and ethical practice, Dr. Reddy's will support publication of the data. This will be done under the responsibility of Dr. Reddy's.

#### **11.1.8 Disclosure and Confidentiality**

By signing the protocol, the investigator agrees to keep all information provided by Dr. Reddy's in strict confidence and to request similar confidentiality from his/her staff and the EC/IRB. Study documents provided by Dr. Reddy's (investigators' brochures, protocols, eCRFs and other protocol-related documents) will be stored appropriately to ensure their confidentiality. The information provided by Dr. Reddy's to the investigator may not be disclosed to others without direct written authorization from Dr. Reddy's, except to the extent necessary to obtain informed consent from subjects who wish to participate in the trial.

#### **11.1.9 Premature Termination or Suspension of the Study**

Both Dr. Reddy's and the investigator reserve the right to terminate the study at any time.

If a study is prematurely terminated or suspended, Dr. Reddy's will promptly inform the investigators, the ECs/IRBs and Health Authorities, as appropriate, and provide the reason(s) for the termination or suspension.

If the study is prematurely terminated or suspended for any reason, the investigator in agreement with Dr. Reddy's should promptly inform the enrolled subjects and ensure their appropriate treatment and follow-up.

In addition, if the investigator terminates or suspends a study without prior agreement of the sponsor, the investigator should promptly inform Dr. Reddy's and the EC/IRB, and should

provide the sponsor and the EC/IRB with a detailed written explanation of the termination or suspension.

If the EC/IRB terminates or suspends its approval/favorable opinion of a study, the investigator should promptly notify Dr. Reddy's and provide Dr. Reddy's with a detailed written explanation of the termination or suspension.

## 11.2 Good Clinical Practice

### 11.2.1 Ethics and Good Clinical Practice

The investigator will ensure that this study is conducted in full conformance with the principles of the "Declaration of Helsinki" (as amended in Tokyo, Venice, Hong Kong, Somerset-West, Edinburgh, Washington DC, Tokyo, Seoul and Fortaleza) and with the laws and regulations of the country in which the clinical research is conducted. A copy of the most recent version of the Declaration of Helsinki will be provided in the investigator site file.

All studies must follow the ICH GCP Guidelines and, if applicable, the Code of Federal Regulations. In other countries in which GCP Guidelines exist, the investigators will strictly ensure adherence to the stated provisions.

### 11.2.2 Ethics Committee / Institutional Review Board

The investigator will submit this protocol and any related document provided to the subject (such as subject information used to obtain informed consent) to an Ethics Committee (EC) or Institutional Review Board (IRB). Approval from the committee must be obtained before starting the study, and should be documented in a dated letter to the investigator, clearly identifying the trial, the documents reviewed and the date of approval. A list of members participating in the meeting must be provided, including the functions of these members. If study staff were present, it must be clear that none of these persons voted.

Modifications made to the protocol after receipt of the EC/IRB approval must also be submitted as amendments by the investigator to the EC/IRB in accordance with local procedures and regulations (see Section 11.1.1).

### 11.2.3 Informed Consent

It is the responsibility of the investigator to obtain written informed consent from each individual participating in this study after adequate explanation of the aims, methods, and objectives of the study and potential hazards of the study drug. The investigator must also explain to the subjects that they are completely free to refuse to enter the study or to withdraw from it at any time for any reason. Appropriate forms for documenting written informed consent will be provided to the sites prior to the study. The Informed Consent and Subject Information will be provided in the local language.

### 11.2.4 Compensation to Subjects and Investigators

Dr. Reddy's is providing insurance in study related bodily injury to the investigator/center/Subject against claims arising from the study, except for claims that arise from malpractice and/or negligence due to QPS (CRO) and Investigator.

## **12 STRUCTURED RISK ANALYSIS**

A risk-benefit analysis was made by Dr. Reddy's Laboratories and part of the submission package.

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## 14 APPENDICES

### 14.1 IGA

**Table 8: IGA Scale**

Score	Definition
0 = Clear	No signs or symptoms present
1 = Near clear	1 or 2 papules
2 = Mild	Some papules and pustules
3 = Moderate	Moderate number of papules and pustules
4 = Severe	Numerous papules and pustules, nodules

### 14.2 CEA

**Table 9: CEA Scale**

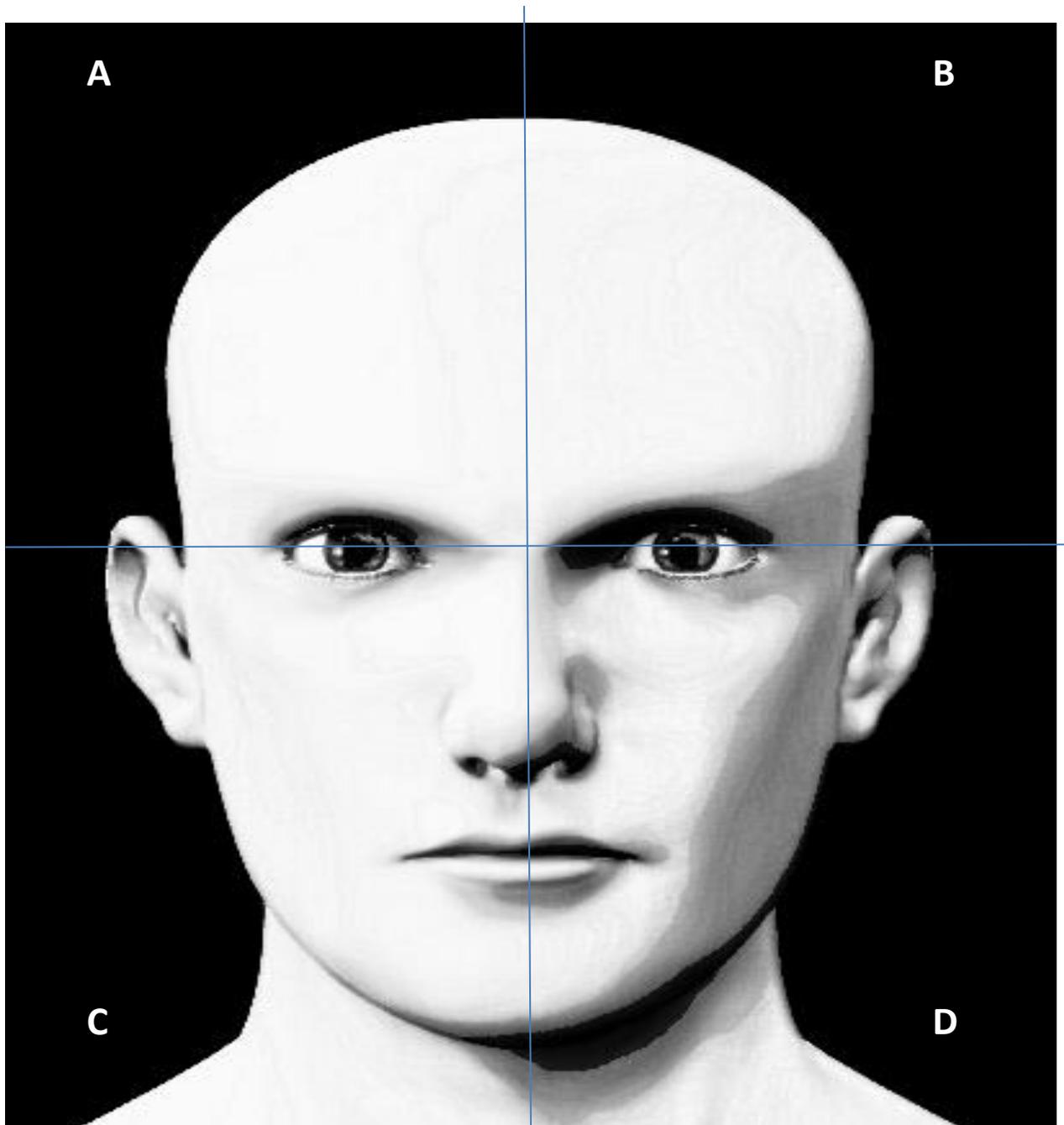
Score	Definition
0 = None	No redness present
1 = Mild	Slight pinkness
2 = Moderate	Definite redness
3 = Significant	Marked erythema
4 = Severe	Fiery redness

### 14.3 Telangiectasia Score

**Table 10: Telangiectasia Score**

Score	Number of Telangiectasias visible
0 = Clear	No telangiectasias
1 = Mild	≤4 telangiectasias
2 = Moderate	5-9 telangiectasias
3 = Severe	≥10 telangiectasias

#### 14.4 Diagram of the Face



Each pustule to be marked by 'X' at its approximate location.  
Each papule to be marked by '□' at its approximate location.  
Each nodule/cyst to be marked by 'O' at its approximate location

**Figure 14-1: Diagram of the Face**

